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Intracranial Subdural Empyema During Long-term Chemotherapy for Metastatic Colorectal Cancer: Case Report

TAKUYA SHIMOGAWA, YUJI MIYAMOTO, YUKIHARU HIYOSHI, MAYUKO OUCHI, KEISUKE KOSUMI, KOJIRO ETO, SATOSHI IDA, MASAAKI IWATSUKI, YOSHIFUMI BABA and HIDEO BABA

Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

Abstract. *Background/Aim: Although chemotherapy for colorectal cancer has advanced remarkably, long-term chemotherapy can lead to a variety of infections. However, if chemotherapy must be discontinued to control infection, there is a risk of progression of colorectal cancer. Intracranial subdural empyema is a life-threatening intracranial infection. The condition requires 6-8 weeks of antibiotic therapy, and the patient must discontinue chemotherapy during treatment. We herein present a case of intracranial subdural empyema during long-term chemotherapy for metastatic rectal cancer. Case Report: A 69-year-old woman with unresectable metastatic rectal cancer had a convulsive seizure and was admitted to our hospital. The cause of the convulsive seizure was considered a metastatic brain tumor from rectal cancer. However, on the basis of contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging, we diagnosed intracranial subdural empyema. The infection was controlled by antibiotics, but chemotherapy for rectal cancer was discontinued during antibiotic treatment. As a result, the rectal cancer progressed, and the patient died 65 days after admission to our hospital. Conclusion: Intracranial subdural empyema may develop rarely during chemotherapy. This condition requires long-term treatment with antibiotics; therefore, early detailed imaging and diagnosis may improve the prognosis.*

Correspondence to: Hideo Baba, MD, Ph.D., Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kumamoto University, 1-1-1 Honjo, Kumamoto 860-8556, Japan. Tel: +81 963735212, Fax: +81 963714378, e-mail: hdobaba@kumamoto-u.ac.jp

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Chemotherapy for colorectal cancer has advanced remarkably, leading to a long-term prognosis for patients with colorectal cancer. However, patients who have undergone long-term systemic chemotherapy sometimes become compromised hosts and can develop unexpected infections. Without early detection and treatment, infections may become life-threatening.

Intracranial subdural empyema is an infection of the membranes surrounding the brain (1) and is a severe condition that can result in brain damage or even death if not treated quickly. This condition often results from otorhinologic infection, head trauma, or cranial surgical procedures (2). However, there are few reports of intracranial subdural empyema in chemotherapy patients (3). The classical triad of subdural empyema includes fever, sinusitis, and neurological deficits (4). Headache, nausea, vomiting, seizures, changes in consciousness, and focal neurological signs are other clinical features (4). The treatments are appropriate antibiotic therapy and timely surgical intervention (4). The differential diagnosis based on the clinical symptoms includes a range of neurologic and infectious diseases, such as brain tumors, stroke, bacterial meningitis, and epidural abscesses (5).

We report a 69-year-old woman who developed intracranial subdural empyema during treatment for rectal cancer with a molecular targeted agent. To our knowledge, this is the first report of intracranial subdural empyema during chemotherapy with a molecular targeted agent.

Case Report

A 69-year-old woman was receiving long-term chemotherapy for unresectable metastatic rectal cancer. Eight years earlier, colonoscopy had revealed a 3/4 circumferential wall thickening with an ulcer located 15 cm from the anal verge (Figure 1A), and colonic biopsy led to a diagnosis of adenocarcinoma. Contrast-enhanced computed tomography (CT) revealed wall thickening at the rectosigmoid junction, with contrast enhancement (Figure 1B), and fluorodeoxyglucose-positron emission tomography showed abnormal uptake in the lesion

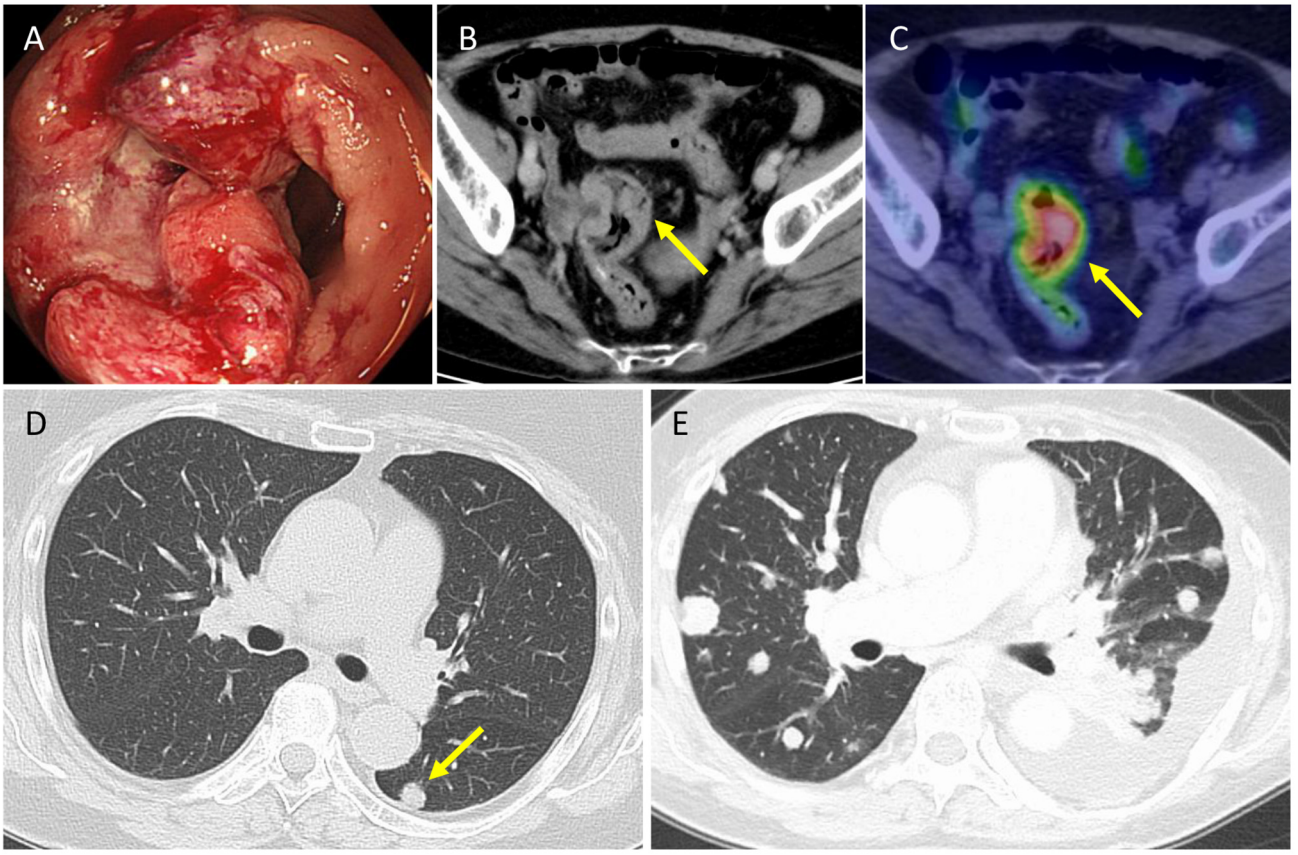

Figure 1. *Imaging during the rectal cancer diagnosis and metastatic recurrence. A) Colonoscopic image showing circumferential wall thickening of the rectum. B) Contrast-enhanced computed tomography (CT) image showing wall thickening of the rectum (arrow). C) Fluorodeoxyglucose-positron emission tomography (FDG-PET) image showing increased FDG uptake in the rectum (arrow). D) CT image two years after surgery showing a metastatic tumor in lung segment 6 of the left lung (arrow). E) CT image eight years after surgery showing multiple metastatic tumors in both lungs and metastasis to the mediastinal lymph nodes.*

(Figure 1C). Therefore, laparoscopic high anterior resection was performed for rectal cancer. The pathological diagnosis was pT4aN2M0 pStage IIIB, and both *RAS* and *BRAF* genes were wild-type. The patient was treated with adjuvant therapy with 5-flurouracil for six months. Two years after surgery, a metastatic lung tumor of rectal cancer appeared in segment 6 of the left lung (Figure 1D), and partial resection of the lower lobe of the left lung was performed. A year and three months later, numerous metastases due to rectal cancer in the lungs and distant lymph nodes were observed (Figure 1E).

Eight years after the first surgery, the patient had a convulsive seizure and was transported to our hospital. The seizure occurred while she was undergoing fourth-line chemotherapy (bevacizumab plus trifluridine/tipiracil hydrochloride). There were no subsequent seizures, but prolonged consciousness disturbance occurred. Head CT showed a low-density area in the right frontal lobe (Figure 2A), and fluid-attenuated inversion recovery head magnetic resonance imaging (MRI) showed a high-signal intensity area in the same region (Figure 2B). However, no abnormal findings were found in the subdural space. Cerebral spinal fluid examination revealed elevated protein, but cytological examination revealed no atypical cells suspicious for rectal cancer metastasis, and no bacteria were isolated on bacterial culture. Electroencephalography also showed no abnormal findings. Blood tests revealed a normal white blood cell (WBC) count [3,700/mm^3 (normal range=3,100-8,400/mm^3)], but C-reactive protein (CRP) levels were high [17.6 mg/l (normal range=0-3 mg/l)]. At first, we suspected cerebral infarction, but there were no abnormalities in the neurological examination other than consciousness disturbance. Based on the blood test results, we considered an infection from an undetermined infectious source and started antibiotic therapy with ampicillin and sulbactam. The patient's consciousness improved within one day, and antibiotics were administered for four days. She was discharged home after seven days of hospitalization.

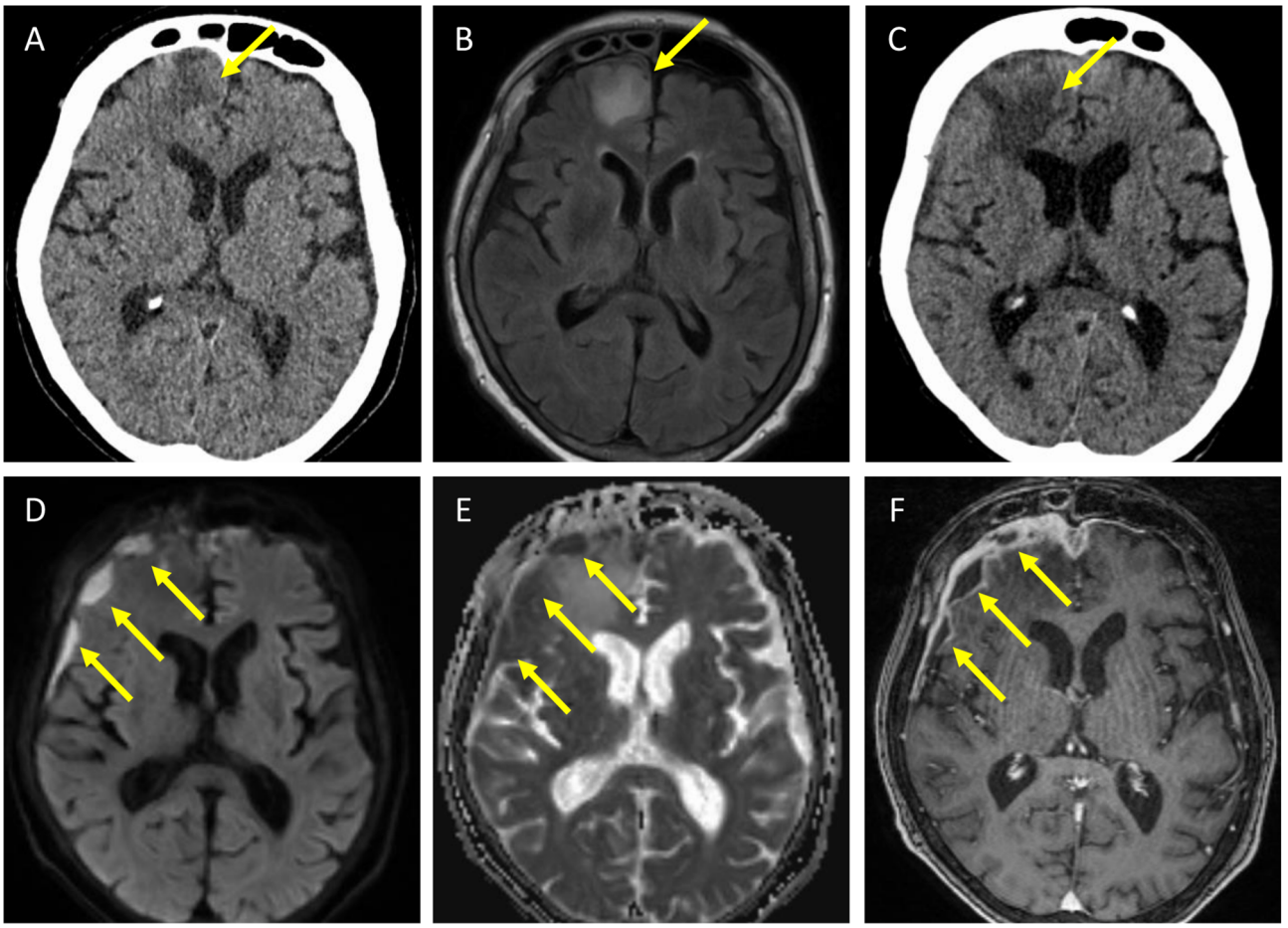

Figure 2. *Imaging of the head before and at the time of the diagnosis of intracranial subdural empyema. A) Head computed tomography (CT) image showing a low-density area in the right frontal lobe (arrow). B) Fluid-attenuated inversion recovery-magnetic resonance imaging (FLAIR MRI) showing a high-signal intensity area in the right frontal lobe (arrow). C) Head CT image showing an enlarged low-density area in the right frontal lobe (arrow). D) Diffusion-weighted MRI showing high-signal fluid collection on the cerebral surface of the right frontal lobe (arrows). E) Apparent diffusion coefficient (ADC) map showing low-signal fluid collection on the cerebral surface of the right frontal lobe (arrows). F) Contrast-enhanced MRI showing capsular formation with a contrast effect (arrows).*

Five months later, she began fifth-line chemotherapy (panitumumab). Twenty days later, she had a second convulsive seizure and was transported to our hospital. Head CT showed an enlarged low-density area in the right frontal lobe compared with previous images six months earlier (Figure 2C). Because the recurrence of rectal cancer was not well controlled, we considered a metastatic brain tumor from rectal cancer. However, diffusion-weighted MRI showed high-intensity signals, and apparent diffusion coefficient mapping showed low-signal intensity fluid collection on the cerebral surface of the right frontal lobe (Figure 2D and E). Contrast-enhanced MRI showed capsular formation with a contrast effect (Figure 2F). Considering the imaging findings, we diagnosed intracranial subdural empyema. Blood tests revealed a high WBC count [14,700/mm^3 (normal range=3,100-8,400/mm^3)] and high CRP levels [25.4 mg/l (normal range=0-3 mg/l)], and antibiotic therapy with ceftriaxone was initiated immediately. The patient's consciousness improved the same day, and blood tests revealed gradually decreasing WBC count and CRP levels to within the respective reference ranges.

Following the patient's improvement, we planned antibiotic therapy for eight weeks to treat the intracranial subdural empyema. However, it was necessary to temporarily discontinue chemotherapy for metastatic rectal cancer during the antibiotic therapy. As a result of failure to continue treatment for the metastatic rectal cancer, the patient developed respiratory failure due to metastatic lung tumor growth and worsened malignant pleural effusion. Therefore, further aggressive treatment was not possible, and the treatment plan was changed to palliative care. The patient died of ascending colon cancer 65 days after her first presentation to our hospital (Figure 3).

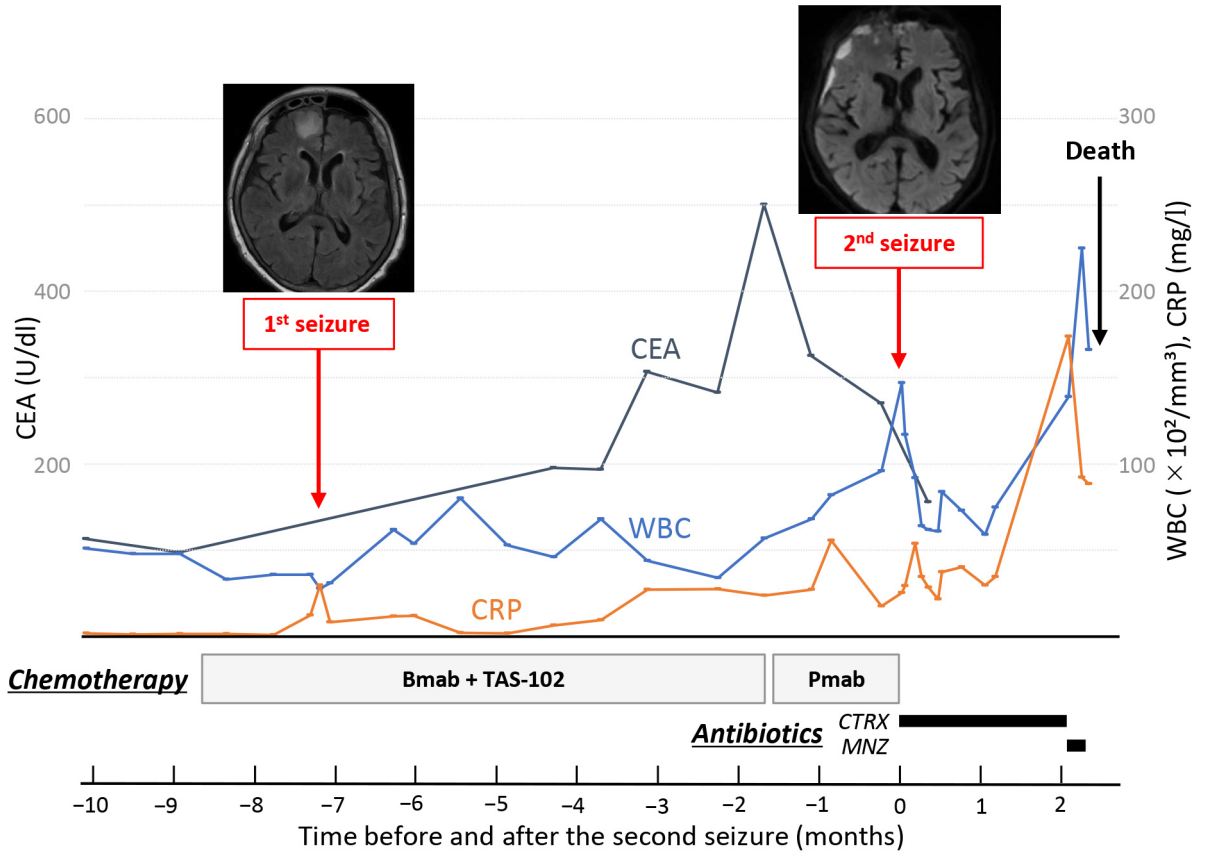

Figure 3. *Changes in carcinoembryonic antigen (CEA), white blood cell (WBC), and C-reactive protein (CRP) after fourth-line chemotherapy. Pmab: Panitumumab; Bmab: bevacizumab; TAS-102: trifluridine/tipiracil hydrochloride, CTRX: ceftriaxone; MNZ: metronidazole.*

Discussion

We report a rare case of intracranial subdural empyema during long-term chemotherapy for unresectable rectal cancer. The intracranial subdural empyema in this case can be attributed to the immunosuppressive effects of long-term chemotherapy, which weakened the patient's immune system and increased her susceptibility to infections.

Prolonged systemic chemotherapy can lead to various infections. Among intracranial infections, brain abscess can result in part from systemic chemotherapy (6). However, there are few reports of intracranial subdural empyema during chemotherapy. Intracranial subdural empyema may be associated with otorhinologic infection, head trauma, or cranial surgical procedures (2). To our knowledge, this is the first report of a patient developing intracranial subdural empyema during chemotherapy, with no history of head trauma or cranial surgical procedures. Systemic chemotherapy leads to an immunocompromised state and increases the risk of developing both intracranial infections and a variety of other infections (7). Our patient most likely developed intracranial subdural empyema owing to immunodeficiency caused by chemotherapy.

Intracranial subdural empyema is a life-threatening disease. This condition is characterized by pus collection in the potential space between the inner layer of the dura mater and the arachnoid mater, accounting for nearly 20% of focal intracranial infections (8). In the era of antibiotics, the mortality rate associated with intracranial subdural empyema has been reduced to approximately 10% (8). Expedited surgical treatment and empirical parenteral antibiotic therapy improve the chances of good neurological outcomes in patients with intracranial infections (9). The antibiotic duration is usually 6-8 weeks (10). In our case, we suspected brain metastasis of rectal cancer the day the patient presented to our hospital. We also suspected infection because blood tests revealed a high WBC count and CRP levels, and we promptly initiated intravenous antibiotics. The patient underwent head CT the day after admission. The next day, she underwent contrast-enhanced head MRI, after which, we diagnosed intracranial subdural empyema for the first time. However, we did not choose surgical treatment because she

had no abnormal neurological findings, and her vital signs and blood test data were improving. In similar cases, if the abscess increases in size or neurological abnormalities appear, we would choose surgical treatment. The patient died of rectal cancer that had progressed during the eight weeks of antibiotic therapy. In this case, surgical treatment was not an option because the prognosis from rectal cancer was not long, and the response to treatment with antibiotics was favorable.

CT and MRI are the primary radiological modalities to detect intracranial infections (11). The imaging signs of subdural empyema and its complications are more readily appreciated on MRI compared with CT. The multiplanar capability of MRI facilitates the detection of subfrontal or subtemporal fluid collections, which are often missed with axial CT (12). In this case, a metastatic brain tumor was suspected on admission, but detailed imaging with contrast-enhanced CT and contrast-enhanced MRI led to the diagnosis of intracranial subdural empyema two days after the patient arrived at our hospital.

Conclusion

During chemotherapy, patients can easily develop infections. In this case, intracranial subdural empyema developed during chemotherapy for rectal cancer. Intracranial subdural empyema requires long-term antibiotic therapy and, when it develops during chemotherapy, the condition can be fatal. Although it is rare for intracranial subdural empyema to develop during chemotherapy, if there are symptoms, such as consciousness disturbance or convulsive seizures, and elevated WBC and CRP, intracranial subdural empyema may be considered a differential diagnosis. Early diagnosis with detailed imaging may improve the prognosis.

Conflicts of Interest

The Authors declare that they have no conflicts of interest in relation to this study.

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Authors' Contributions

TS described and designed the study. YM edited the manuscript. HB supervised the editing of the manuscript. YH and YM performed the surgery. MO, KK, KE, SI, MI, and YB read and approved the final manuscript.

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