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Successful treatment with metronidazole and paromomycin for fulminant amoebic colitis during cytotoxic chemotherapy in a patient with small-cell lung cancer

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ABSTRACT

We report the case of a 64-year-old man with advanced small-cell lung cancer who developed fulminant amoebic colitis during cytotoxic chemotherapy. During the first cycle of carboplatin/etoposide treatment, febrile neutropenia and grade 4 neutropenia developed. Because diarrhea, abdominal pain, and bloody stool were observed, abdominal computed tomography was performed, showing intussusception, and extensive colectomy and colostomy were performed. Histopathology of the colon revealed gastrointestinal necrosis and perforation due to *Entamoeba histolytica* infection. Amoebiasis improved after treatment with metronidazole and paromomycin. The second cycle of carboplatin/etoposide with dose reduction was completed, resulting in a partial response to small-cell lung cancer.

The results of this case suggest that paromomycin is an additional option for amoebiasis during cytotoxic chemotherapy, and persistent diarrhea during cytotoxic chemotherapy should alert clinicians to consider the development of amoebiasis.

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Introduction

Amoebiasis is orally transmitted and causes symptoms such as diarrhea, abdominal pain, and bloody stools. Asymptomatic infections or mild cases are usually treated with oral medications. However, necrosis of the large intestinal mucosa and perforation of the gastrointestinal tract may occur, requiring surgical treatment. Here, we report a case of fulminant amoebic colitis as a result of asymptomatic infection by *Entamoeba histolytica*, activated by cytotoxic chemotherapy for small-cell lung cancer (SCLC).

Case report

A 64-year-old man was referred to our hospital because of cough and chest X-ray findings with right pleural effusion and a right hilar mass. Significant facial edema was observed, and chest computed tomography (CT) showed superior vena cava (SVC) syndrome (Fig. 1A,B). A transbronchial biopsy was performed 3 days before chemotherapy and confirmed the diagnosis of SCLC histologically (Fig. 1C-F). A whole-body search indicated right hilar, mediastinal, right supraclavicular, aortic, and superior mediastinal lymph node metastasis and pleural effusion. Enhanced brain magnetic resonance imaging revealed no brain metastases. No abnormal findings were found in the abdomen. The patient was diagnosed with extensive SCLC.

Carboplatin (area under the curve [AUC] 6 $mg \cdot mL^{-1} \cdot min^{-1}$) with etoposide (100 $mg \cdot m^{-2}$) was started as the first-line treatment. Right pneumothorax was observed on the 4th day, and chest tube drainage was initiated. Ampicillin/sulbactam was empirically administered on the 6th day since fever and right thoracic empyema developed. However, febrile neutropenia (159·μL^{-1}) developed on the 8th day, and treatment was empirically changed to meropenem with filgrastim. Although pleural effusion culture showed a meropenem-sensitive peptostreptococcus infection, the patient's condition did not

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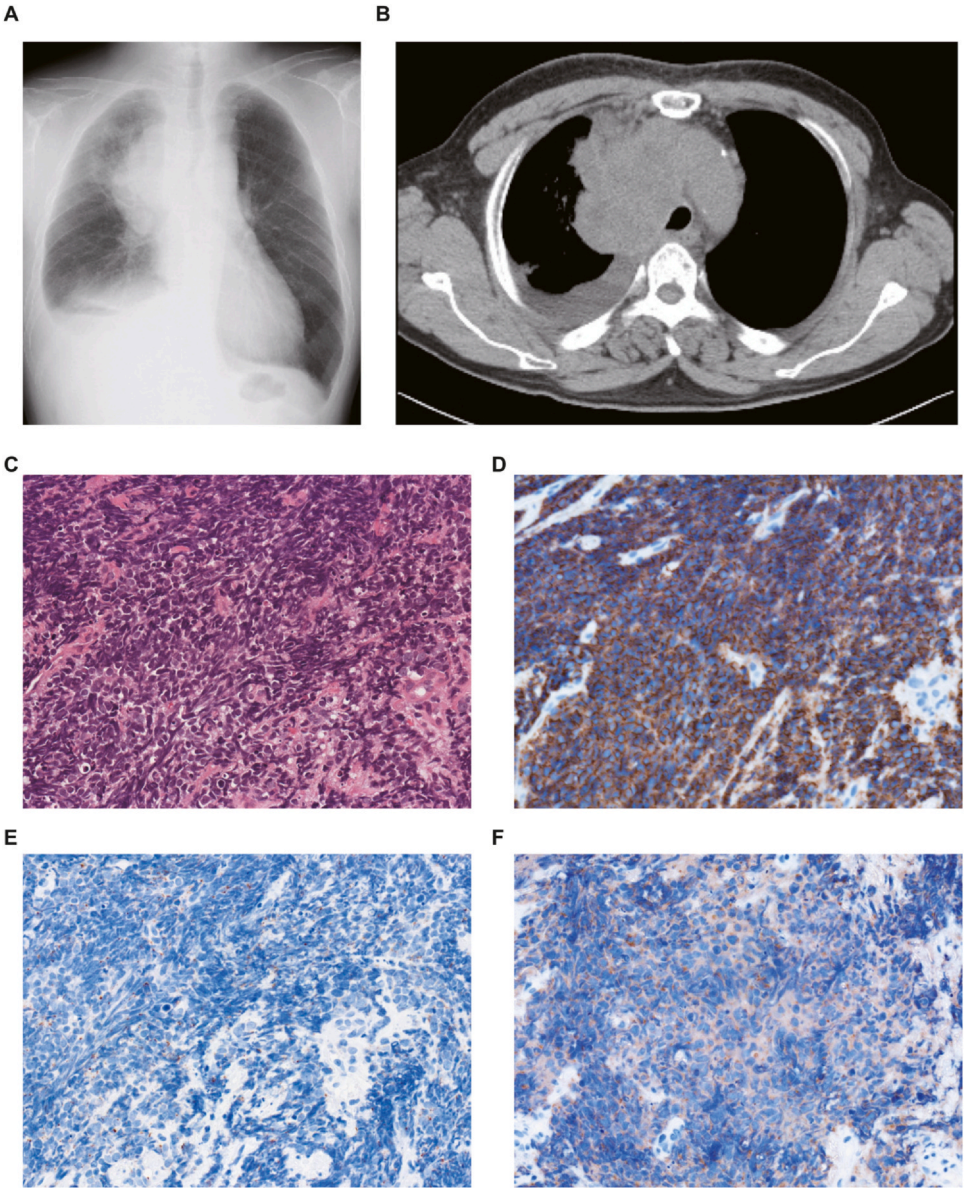

Fig. 1. Chest X-ray (A) and computed tomography (B) showed a large mass with lymph nodes in the right hilar region and pleural effusion. Histological findings of the transbronchial biopsy of the tumor showing small-cell lung cancer. H&E x400 (C), CD56×400 (D), chromogranin A x400 (E), synaptophysin x100 (F). H&E, Hematoxylin and eosin.

improve, and diarrhea appeared on the 19th day. The results of fecal culture, including *Clostridium difficile* (CD) toxin and CD antigen, were negative. Diarrhea and fever persisted, and white blood cell counts surged on the 21st day. Bloody stools and abdominal pain developed on the 24th day. Abdominal CT showed a small amount of ascites, intestinal retention, intussusception in the ileocecal region, and abscess in the left hepatic lobe (Fig. 2A, B). Because ileus and intestinal perforation were suspected, emergency surgery was performed on the 25th day. Intraoperative findings showed extensive necrosis of the colon, and extensive colectomy and colostomy were performed. After the operation, septic shock occurred and intensive care management was performed. Although meropenem was empirically changed to piperacillin/tazobactam, vancomycin, and micafungin to deal with possible catheter related blood stream infection of methicillin-resistant *Staphylococcus aureus* (MRSA) and fungus, fever and systemic inflammation continued. Portal vein thrombosis developed on the 28th day, and anticoagulation therapy was initiated. Pathological specimens revealed *Entamoeba histolytica* trophozoites on the colon, severe inflammatory cell infiltration of the entire layer of the intestinal wall, abscess formation accompanied by bleeding and fibrin in some parts, and loss of continuity of the intestinal wall (Fig. 3). Based on these results, we diagnosed amoebic colitis leading to gastrointestinal perforation, liver abscess, and portal vein thrombosis. In the interviews with the patient, there was no history of amoebiasis nor sexual intercourse with homosexuals, commercial sex workers, or an unspecified number of people. He had traveled to the Philippines seven years before the onset of symptoms and to the West Coast of the United States, Hawaii, and Shanghai 10 years previous. Thus, he might have been affected by asymptomatic amoebiasis, and cytotoxic chemotherapy activated the amoebiasis.

Metronidazole was given orally from the 33rd to the 42nd day, and the patient's general condition improved. The size of the liver abscess was 36 mm x 30 mm, and it was difficult to perform percutaneous catheter drainage. Bacterial culture of the right pleural effusion was negative on the 49th day, and the chest tube was removed. Pleural effusion culture was performed multiple times, but no *Entamoeba histolytica* was detected. Because chemotherapy for SCLC was scheduled, oral treatment with paromomycin was

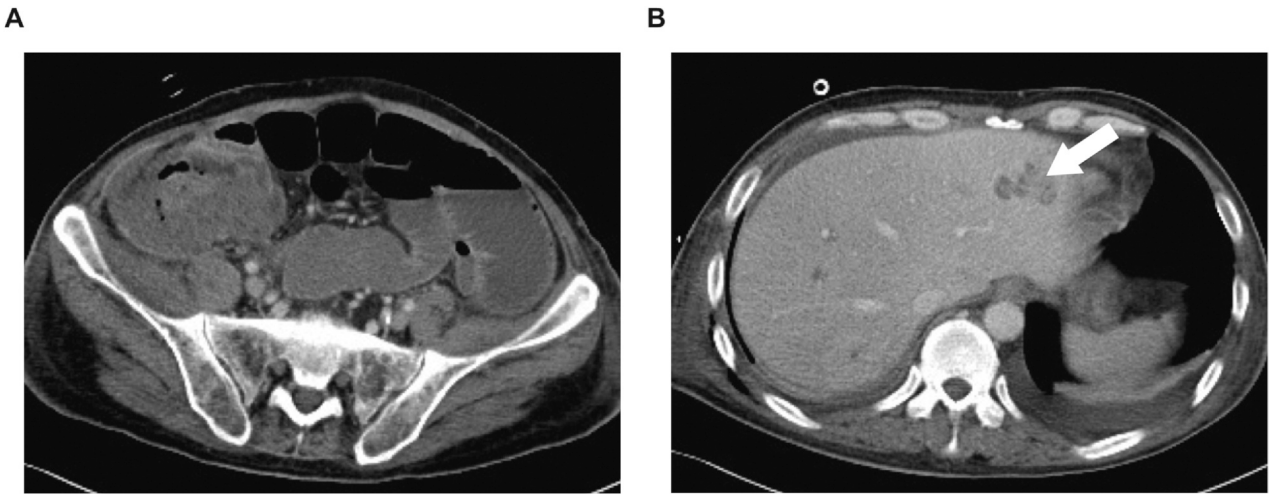

Fig. 2. Abdominal computed tomography on the 24th day showed intestinal dilatation and ileocecal stacking (A) and 36 mm × 30 mm liver abscess in the left of the liver (B, a white arrow).

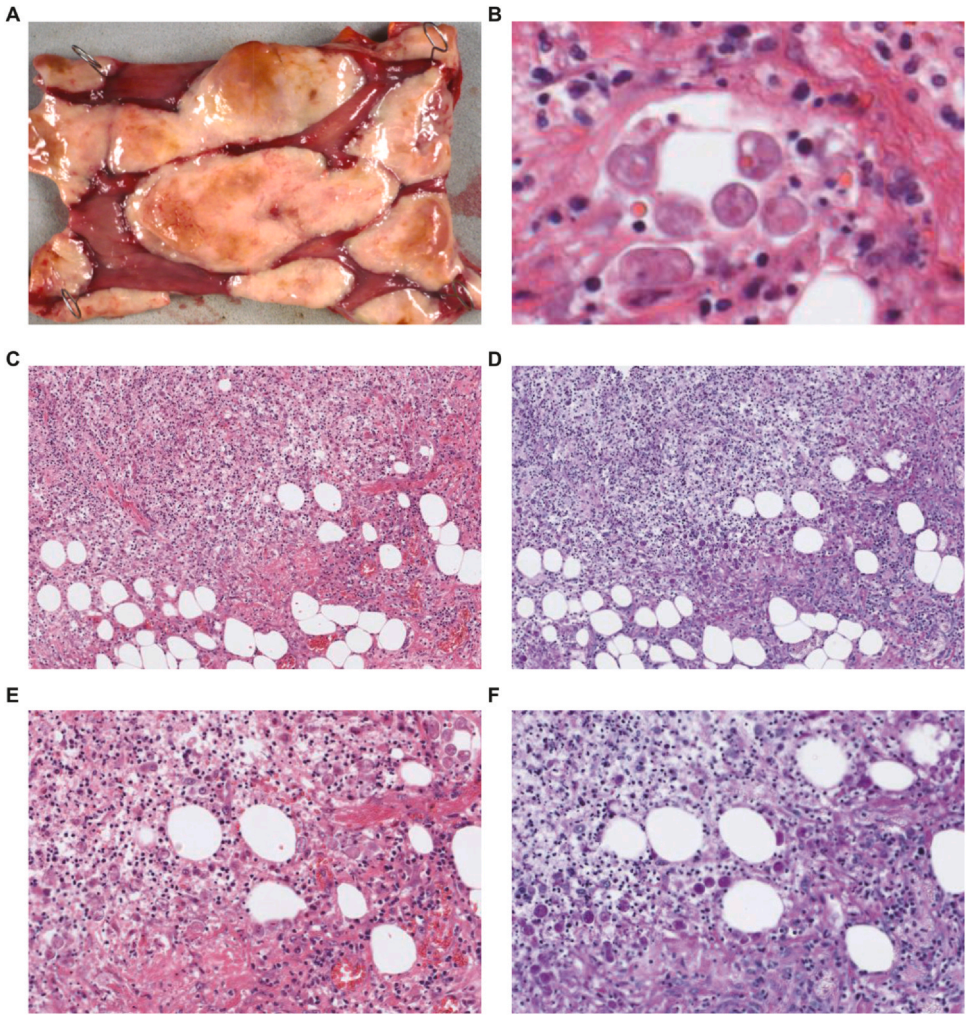

Fig. 3. Macroscopic pathology of the resected colon showed multiple ulcerative lesions (A). Histological findings of the surgically resected colon showing inflammatory infiltrate *Entamoeba histolytica* trophozoites and erythrophagocytosis (B, H&E x400). H&E x40 (C), PAS x40 (D), H&E x100 (E), PAS x100 (F). H&E, Hematoxylin and eosin; PAS, Periodic acid-schiff.

administered for 10 days from the 43th day as anti-cystic therapy to prevent recurrence of amoebiasis. Lower gastrointestinal endoscopy was performed on the 61st day. The lumen showed mild white mucus and residual redness, and the biopsy detected the carcasses of amoebic trophozoites. The patient's general condition improved, and the liver abscess shrank on the abdominal echo findings. Therefore, we concluded that the amoebic dysentery was cured (Fig. 4).

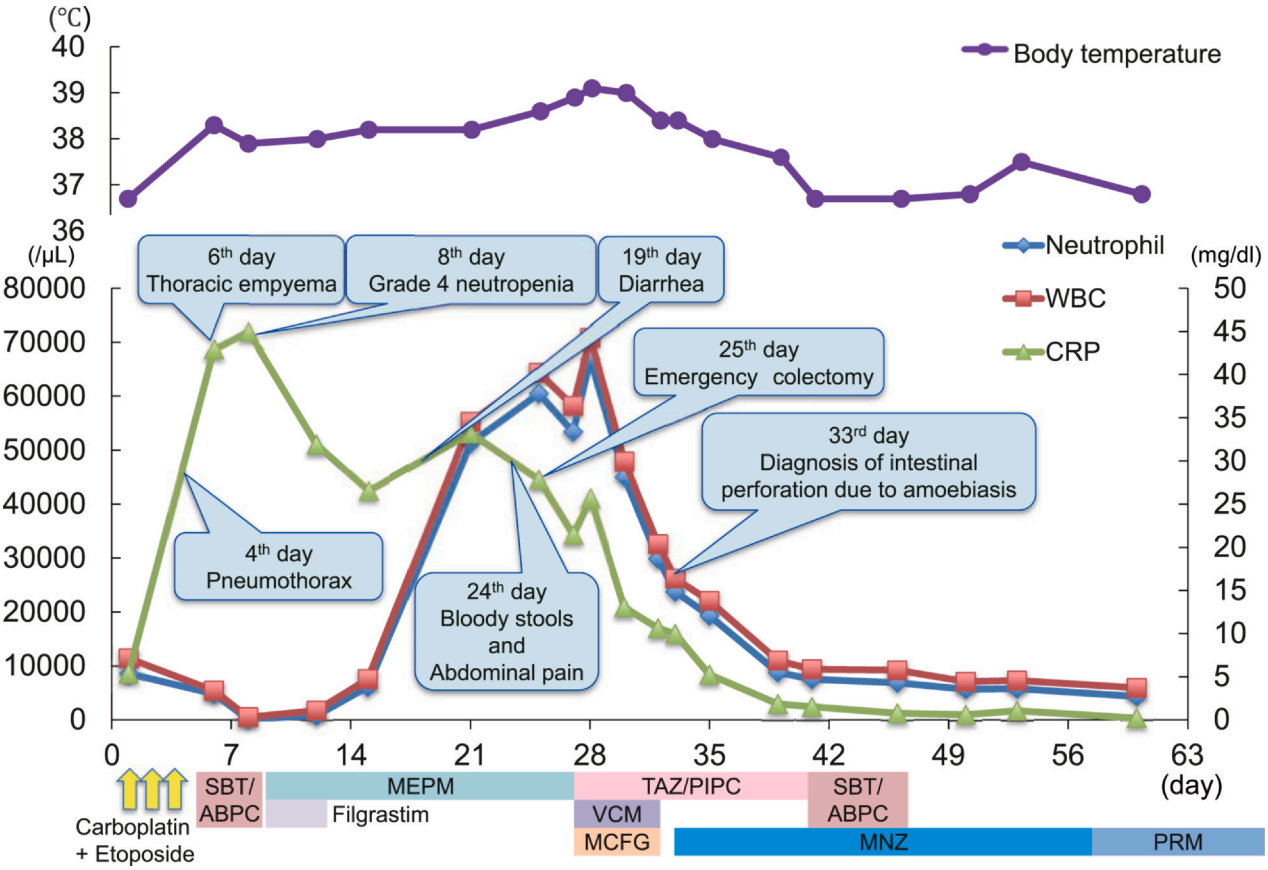

Fig. 4. Summary of clinical course. WBC, white blood cell; CRP, C-reactive protein; SBT/ABPC, Sulbactam and ampicillin; MEPM, meropenem; TAZ/PIPC, tazobactam and piperacillin; VCM, vancomycin; MCFG, micafungin; MNZ, metronidazole; PRM, paromomycin.

Palliative radiotherapy was performed from the 59th to 69th day because the SVC syndrome had exacerbated. The second cycle of chemotherapy for lung cancer was initiated with a dose reduction of carboplatin (AUC 5 mg·mL^{-1}min^{-1}) with etoposide (75 mg·m^{-2}) on the 84th day. Four cycles of chemotherapy were completed with a partial response. There was no recurrence of amoebic dysentery during the treatment.

Discussion

Amoebiasis is a disease caused by infection with *Entamoeba histolytica* and is common in developing countries. In developed countries, it is only common in the case of homosexuals, commercial sex workers, persons with intellectual disabilities, or persons returning from travel to developing countries. The route of infection is mainly fecal-oral infection, often derived from ingestion of water or food and drink contaminated with cysts, but is also known as a sexually transmitted disease [1]. Approximately 90–95% of people infected with *Entamoeba histolytica* have only asymptomatic infection or extremely mild diarrhea, and less than 10% have clinical symptoms. Amoebiasis sometimes becomes severe and is activated under immunosuppressive conditions, such as administration of steroids and anticancer drugs, and as a result of acquired immunodeficiency syndrome [2]. Eighteen human immunodeficiency virus type 1 infected individuals developed invasive amoebiasis among 1207 patients who had no history of amoebiasis [3]. The incubation period of amoebic appendicitis ranged from months to years [4].

Thus, it is difficult to diagnose amoebic dysentery in a developed country during hospitalization because of long incubation period of amoebiasis. Although the precise route of infection was unknown in the case of our patient, it is possible that he was infected with *Entamoeba histolytica* when traveling abroad, became an asymptomatic carrier, and developed amoebiasis under immunosuppression by cytotoxic chemotherapy. Fulminant amoebiasis during antineoplastic treatment occurs in asymptomatic carriers and sometimes leads to amoebiasis-related death [5,6]. Therefore, it is important to check the travel history and medical history for evidence of amoebic dysentery before initiating cytotoxic chemotherapy.

Amoebiasis is classified into intestinal amoebiasis and extraintestinal amoebiasis. Intestinal amoebiasis typically presents as mucous stools, diarrhea, and tenesmus. The mortality rate of fulminant necrotizing intestinal amoebiasis with perforation is more than 50%, even with surgical intervention [7]. Liver abscess is the most common form of extraintestinal amoebiasis, resulting in fever, general malaise, night sweats, and right pleurisy. Our patient presented with fulminant amoebic diarrhea resulting in septic shock due to extensive full-thickness necrosis of the large intestine and perforation of the intestinal tract.

Both intestinal amoebiasis and extraintestinal amoebiasis are treated with antiprotozoal agents, such as metronidazole [2]. When invasive infections are treated with metronidazole alone without a cyst extermination drug, such as paromomycin, 40%– 60% of the patients become cyst carriers [8]. All the cases of invasive amebiasis, including amebic dysentery, should be treated with cyst extermination drugs, following antiprotozoal agents. Although in two cases of lung adenocarcinoma and hypopharyngeal cancer, the patients were able to continue cytotoxic chemotherapy after treatment of amoebiasis without anti-cystic therapy [9,10], paromomycin may

be effective in ensuring that the luminal parasites are cleared to prevent relapse [11]. Therefore, we used paromomycin before the next stage of cytotoxic chemotherapy, and there was no recurrence during treatment.

In conclusion, the results of this case suggests that paromomycin is an additive option for amoebiasis during cytotoxic chemotherapy, and persistent diarrhea during cytotoxic chemotherapy should alert clinicians to consider the development of amoebiasis.

Ethical approval

The case report had been prepared in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the Kishiwada City Hospital.

Consent

Written informed consent was obtained.

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CRediT authorship contribution statement

Aya Kitaoka: Writing – original draft. **Kazuya Tanimura:** Conceptualization. **Yuto Yasuda:** Writing – review & editing. **Kensuke Nishioka:** Resources. **Yutaka Hirayama:** Resources. **Kiyoshi Uemasu**: Investigation. **Daisuke Iwashima**: Investigation. **Sou Arita:** Resources. **Toshiyuki Kitai:** Resources. **Susumu Hoshi:** Resources. **Emi Date:** Visualization. **Norishige Iizuka:** Visualization. **Ken-ichi Takahashi:** Supervision.

Consent for publication

Written informhe patient for the publication of this report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Competing interests

The authors have no conflicts of interest directly relevant to the content of this article.

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