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【 CASE REPORT 】

Pneumatosis Intestinalis in Lung Cancer Induced Twice by Different Drugs: Bevacizumab and Pemetrexed

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Abstract:
A 72-year-old man diagnosed with stage 4 lung adenocarcinoma developed asymptomatic pneumatosis intestinalis while undergoing treatment with first-line chemotherapy, which included carboplatin, paclitaxel, and bevacizumab (BEV). He was treated conservatively. The pneumatosis recurred while the patient was undergoing treatment with the third-line chemotherapy, which included pemetrexed (PEM). His condition resolved after 4 weeks of supportive therapy. To our knowledge, this is the first case in which pneumatosis intestinalis was induced twice by two drugs in a patient with lung cancer. BEV and PEM are often administered to patients with lung cancer; thus, it should be noted that pneumatosis intestinalis may occur as an adverse event in patients treated with these drugs.

Key words: pneumatosis intestinalis, bevacizumab, pemetrexed, lung cancer

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Introduction

Pneumatosis intestinalis is an uncommon but significant illness in which gas is found in a linear or cystic form in the submucosa or subserosa of the bowel wall (1). It is caused by various factors, including pulmonary disease, gastrointestinal disease, and collagen disease. In recent years, the occurrence of pneumatosis intestinalis has been reported to be associated with drugs such as cytotoxic anticancer drugs and molecular targeted drugs. However, to our knowledge, no cases have been reported in which pneumatosis intestinalis developed twice in association with two different drugs. We herein report a case of pneumatosis intestinalis that was first caused by bevacizumab (BEV), which then relapsed during treatment with a cytotoxic chemotherapeutic agent: pemetrexed (PEM).

Case Report

A 72-year-old man visited our hospital to investigate the cause of left lateral chest pain. He had a 5-year history of hypertension and dyslipidemia and no history of allergic disease. He had smoked 20 cigarettes per day for 52 years. He was diagnosed with lung adenocarcinoma (cT3N0M1a, Stage 4) (2). No metastatic lesions in the intestinal tract were observed on positron emission tomography/computed tomography. Because the tumor was negative for epidermal growth factor receptor gene mutation and anaplastic lymphoma kinase fusion gene, he received three cycles of chemotherapy consisting of carboplatin (CBDCA, AUC 5), paclitaxel (PTX, 200 mg/m^2), and BEV (15 mg/kg). When he was hospitalized to receive the fourth cycle of chemotherapy, abdominal CT revealed abdominal free air and pneumatosis intestinalis.

At the time of his admission, his vital signs were normal and no abdominal abnormalities were observed. His white blood cell count was normal (3,940 cells/μL) and his serum C-reactive protein was slightly increased (1.24 mg/dL). Chest radiography showed no evidence of free air. Abdominal CT showed intra-abdominal free air around the liver (Fig. 1A), and pneumatosis in the intestinal wall (Fig. 1B, C). Thus, because we observed no causative factors of pneumatosis intestinalis other than BEV, we diagnosed the patient with pneumatosis intestinalis due to BEV treatment. Intraportal venous gas was not observed. We did

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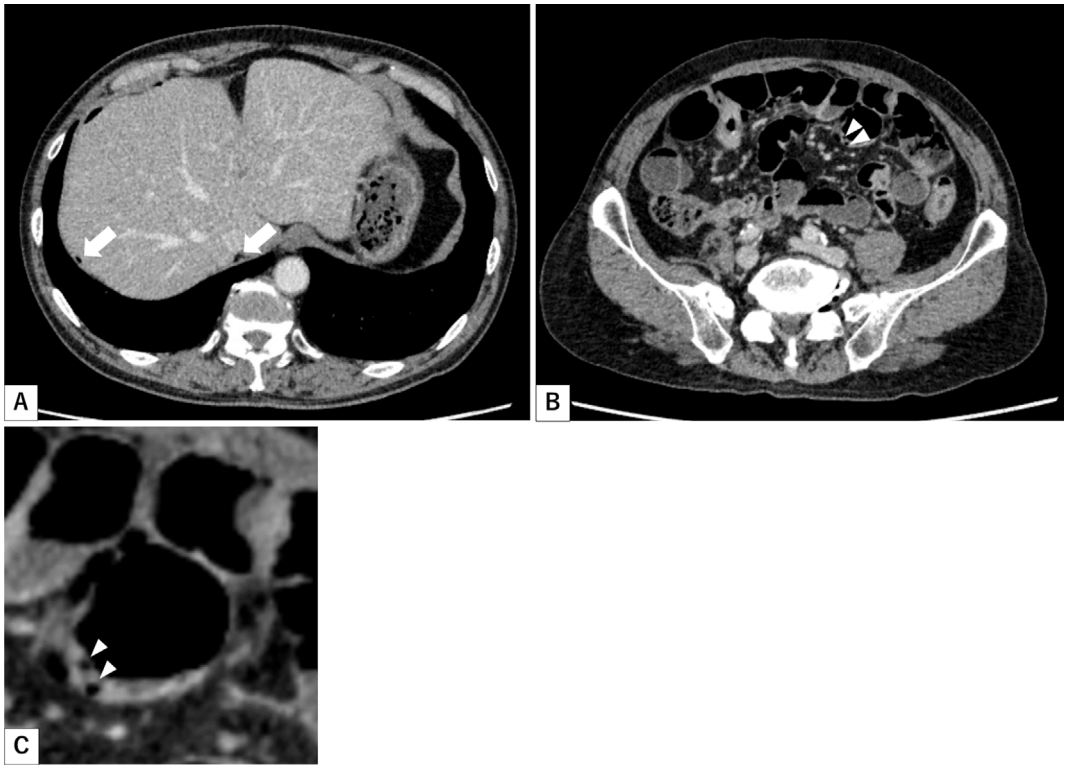

Figure 1. **Abdominal CT on admission after three cycles of carboplatin, paclitaxel, and bevacizumab revealed intra-abdominal free air (arrows) on the liver surface (A), and pneumatosis (arrowheads) in the intestinal wall (B, C).**

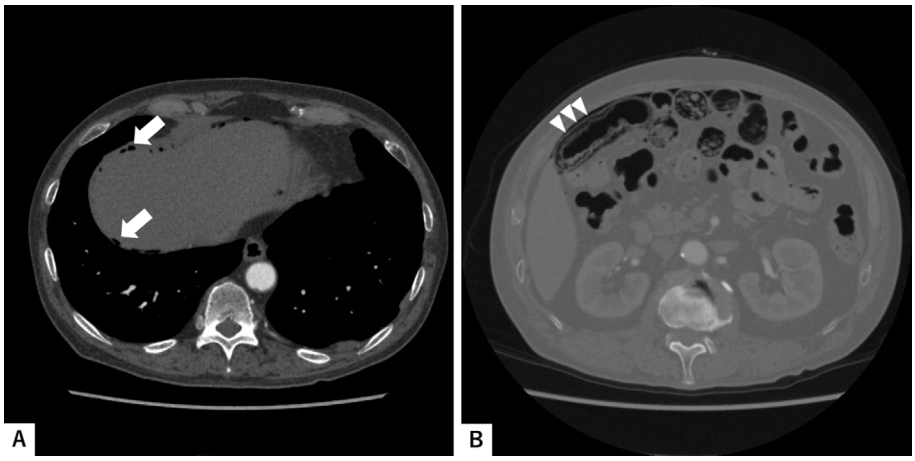

Figure 2. **Abdominal CT under treatment with pemetrexed showed recurrence of intra-abdominal gas (arrows) around the liver (A) and pneumatosis intestinalis (arrowheads) (B).**

not perform a blood gas analysis and could not detect the presence or absence of acidosis. Since he had no symptoms, we discontinued the fourth chemotherapy cycle and treated the patient conservatively with observation.

Abdominal symptoms were not present during follow-up, and abdominal CT revealed that the intra-abdominal free air and pneumatosis had disappeared. CBDCA (AUC 5) and PTX (200 mg/m^2) chemotherapy was initiated, with the patient receiving three cycles of the regimen. Follow-up chest CT revealed progressive disease. Treatment with PEM (500 mg/m^2) was initiated as a third-line therapy. After two cycles of this regimen, intra-abdominal free air appeared on chest radiography. Abdominal CT revealed the recurrence of intra-abdominal gas and pneumatosis intestinalis (Fig. 2). Again, he did not have any other symptoms. Lower gastrointestinal endoscopy showed protruded lesions resembling a submucosal tumor in the center of the transverse colon, which was soft and movable. It was thought to be consistent with pneumatosis intestinalis (Fig. 3). The administration of PEM was stopped, and he was managed supportively. He remained asymptomatic and follow-up CT showed that the intra-abdominal free air and pneumatosis had nearly resolved. Af-

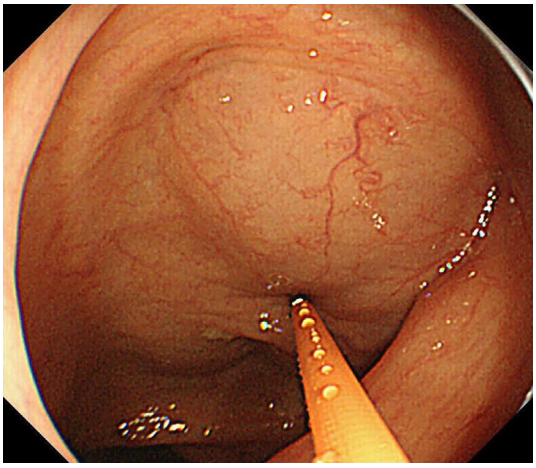

Figure 3. Lower gastrointestinal endoscopy showed soft and movable protruded lesions resembling a submucosal tumor in the center of the transverse colon.

ter that, he was treated with a tegafur-gimeracil-oteracil combination therapy (TS-1, one cycle of 120 mg/day and two cycles of 80 mg/day). However, the malignant lesions were exacerbated and he died of lung cancer 15 months after the diagnosis.

Discussion

Pneumatosis intestinalis is thought to be an infrequent but critical illness. It is reported to manifest as gas found in a linear or cystic form in the submucosa or subserosa of the bowel wall (1). Pneumatosis intestinalis is associated with various conditions, such as pulmonary disease (3, 4), gastrointestinal disease (4), collagen disease (4-6), infectious disease (7, 8), and iatrogenic disorder (9). Moreover, pneumatosis intestinalis is found in association with the use of certain drugs, including steroids (4, 5, 10, 11) and α-glucosidase inhibitors (5, 12).

Recently, several molecular targeted drugs have been reported to be associated with pneumatosis intestinalis, including gefitinib (13), sorafenib, and sunitinib (14). Asmis et al. reported the case of a patient with a low-grade neuroendocrine tumor originating from the pancreas, who presented pneumatosis intestinalis while receiving systematic chemotherapy plus BEV (15). Shinagare et al. reported that 24 cancer patients treated with molecular targeted therapy developed pneumatosis or intestinal perforation. Among these patients, 10 patients had pneumatosis intestinalis, and BEV (n=5) was the drug most commonly associated with pneumatosis in this study (16). Moreover, Lee et al. reported that BEV was administered to 6 of 84 patients in whom pneumatosis intestinalis was identified by CT (17).

Our patient had no relevant medical history and was not using any medications that might have caused pneumatosis intestinalis during his clinical course before chemotherapy. Pneumatosis intestinalis was found three months after the administration of BEV, and there were no findings that could be considered causative other than BEV. We considered that adverse events of BEV, such as gastrointestinal perforation, fistula formation, and wound healing (18), might be associated with pneumatosis intestinalis.

The second occurrence of pneumatosis intestinalis was revealed during chemotherapy with PEM. The patient received a definitive diagnosis following lower gastrointestinal endoscopy at that time. During the time between his first improvement and the recurrence of pneumatosis intestinalis, dexamethasone (1 mg per day; per oral) was administered to relieve the fever caused by lung cancer inflammation. However, dexamethasone continued to be administered until the end of his life, and pneumatosis intestinalis did not occur again after the improvement of the second occurrence. Moreover, he showed no onset of new disease or change in prescription medications except for the addition of dexamethasone. Consequently, we concluded that the second occurrence of pneumatosis intestinalis was associated with PEM.

Several reports have mentioned that cytotoxic chemotherapeutic agents, including etoposide (19), fluorouracil (20), methotrexate (5, 11), irinotecan, and cisplatin (21) might cause pneumatosis intestinalis. Yamamoto et al. reported the case of a patient with lung cancer who was treated with PEM and erlotinib who subsequently developed pneumatosis intestinalis (22). However, to our knowledge, the case reported here is the only report of pneumatosis intestinalis due to PEM alone. Furthermore, to our knowledge, this is the first reported case of pneumatosis intestinalis that appeared twice at different times as a result of treatment with two different drugs.

Although the mechanism of pneumatosis intestinalis is unclear, multiple causes are likely to contribute to the pathogenesis of this disease. Some have suggested mechanical causes arising from gas entering the wall of the bowel, either from the luminal surface of a mucosal fissure due to increased pressure, increased peristalsis and mucosal breaks, or through the mesentery. Others have proposed that the origin may lay in gas-producing bacteria that invade the bowel wall, and that the resulting excessive hydrogen gas leads to pneumatosis intestinalis (23, 24). Moreover, it is hypothesized that exposure to alkyl halides, such as chloral and trichloroethylene enhance hydrogen production and the formation of gas cysts (25).

BEV is a monoclonal antibody that specifically binds vascular endothelial growth factor. This inhibition leads to a reduction in the microvascular growth of tumor blood vessels and thus limits the blood supply to tumor tissues (18). PEM is an antimetabolite that inhibits at least three enzymes involved in the metabolism of folate, which is the mechanism of cytotoxicity of PEM. However, mucositis may occur as an adverse event in patients treated with PEM (26).

The precise mechanisms by which BEV and PEM cause pneumatosis intestinalis are not clear. In the present case, we hypothesize that the decrease in vasculature induced by BEV led to ischemia, causing mucosal breaks and increased

pressure, leading to pneumatosis intestinalis. Furthermore, micro-intestinal hemorrhage and micro-intestinal perforation may have occurred. We should have considered the possibility of recurrence of intestinal emphysema after the administration of BEV. Previous reports have shown that the recurrence rate of intestinal emphysema is 30-40% (1). PEM may have caused pneumatosis intestinalis due to disorder of the intestinal mucosa. Pneumatosis intestinalis had been reported to be attributed to methotrexate (5, 11), and the inhibition of folate metabolism might contribute to the development of pneumatosis intestinalis. Moreover, a combination of factors can lead to pneumatosis intestinalis (4, 5, 11), and in our case, a history of pneumatosis intestinalis due to BEV and steroid therapy may have accelerated the onset of pneumatosis intestinalis by PEM.

Possible treatments of pneumatosis intestinalis include emergency surgery, observation, and medical treatment of the underlying disease (27). Observation is recommended for asymptomatic cases or those with no critical findings. Treatment of underlying disease is necessary for patients with a significant past medical history (27). In the present case, the diagnosis was pneumatosis intestinalis due to BEV and PEM, so we discontinued both drugs. Additionally, the patient was asymptomatic at the onset of the disease, and a physical examination and CT showed only free abdominal air, without bowel perforation, obstruction, or necrosis. As a result, we treated him conservatively. However, because of the occurrence of pneumatosis intestinalis, we needed to discontinue the use of anticancer agents, such as BEV and PEM, which were expected to be effective for his lung cancer. This resulted in a narrowing of the treatment options for lung cancer, which may in turn have affected his prognosis.

There are many opportunities to use molecular targeted drugs, including BEV and cytotoxic anticancer drugs such as PEM. Although pneumatosis intestinalis is rare, it is important to consider pneumatosis intestinalis as a possible adverse event in patients treated with these drugs.

The authors state that they have no Conflict of Interest (COI).

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