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【 CASE REPORT 】

Crizotinib-induced Rectal Perforation with Abscess

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Abstract:
An 86-year-old Japanese man was diagnosed with stage IV lung adenocarcinoma. The patient was treated with crizotinib after echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK) rearrangement was detected from his pleural effusion. He subsequently developed abdominal pain and rebound tenderness in the right lower abdomen. Contrast-enhanced abdominal CT showed a low-density area in the abdominal cavity. The size of the abscess was decreased by drainage and the administration of antibiotics. Fistulography revealed a fistula from the rectum to the abscess, and a diagnosis of lower intestinal tract perforation with abscess formation was made. Crizotinib was discontinued and treatment with alectinib was initiated. The patient remains under treatment as an outpatient at our department without adverse effects.

Key words: ALK rearrangement, crizotinib, non-small cell lung cancer, intestinal tract perforation, alectinib

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Introduction

Crizotinib, an anaplastic lymphoma kinase (ALK) inhibitor that is approved for the use in the treatment of inoperable advanced (stage IIIB/IV)/relapsed disease in patients with echinoderm microtubule-associated protein-like 4 (EML4)-anaplastic lymphoma kinase (ALK)-rearrangement-positive non-small cell lung cancer (NSCLC), is preferred as an initial therapy due to its efficacy and tolerability. Recently, however, cases of gastrointestinal tract side effects have been reported, including severe esophagitis and esophageal ulceration. Our patient developed lower intestinal perforation with intraabdominal abscess in association with the administration of crizotinib. We should be careful about the development of severe adverse events during crizotinib treatment, especially in elderly patients.

Case Report

An 86-year-old Japanese man who was a former smoker was referred to our department to undergo evaluation and treatment for cough, which had developed 2 months previously. Chest computed tomography (CT) revealed a tumor in the right lower lobe with associated pleural effusion (Fig. 1).

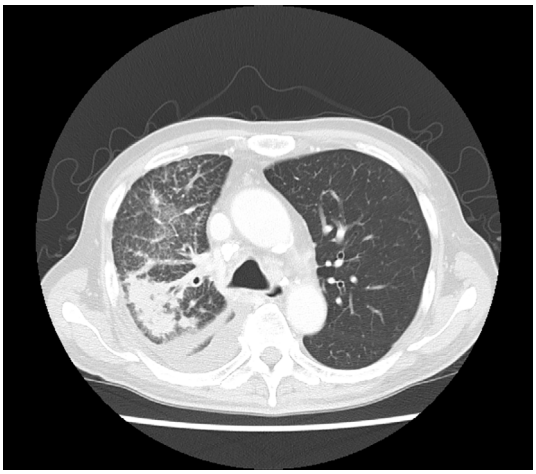

Figure 1. Chest CT showing consolidation in the right S2 segment and pleural effusion.

A cytological examination of the pleural effusion revealed lung adenocarcinoma. No epidermal growth factor receptor (*EGFR*) mutations were found. The patient received one cycle of chemotherapy with carboplatin and pemetrexed as a first-line treatment. This was eventually discontinued due to

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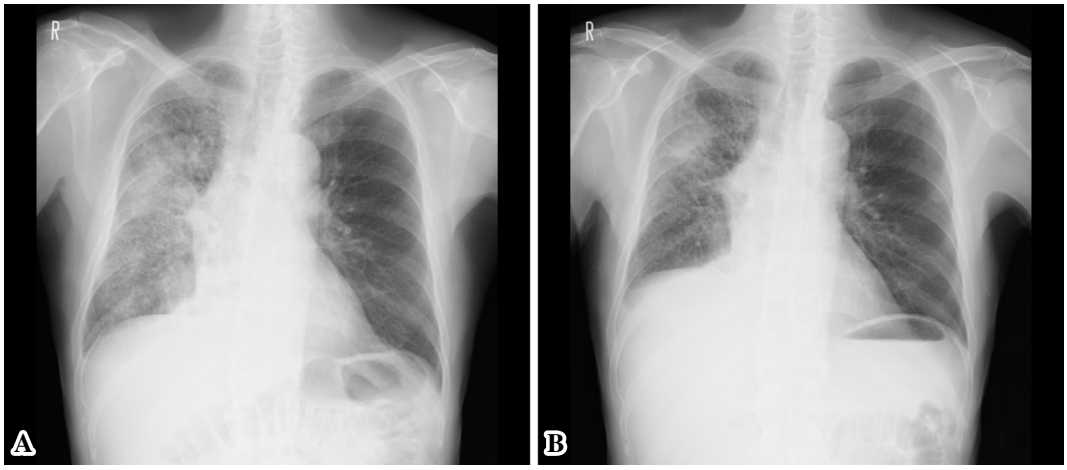

Figure 2. **A: Chest X-ray before crizotinib therapy showed consolidation and ground glass opacity in the right midlung. B: Chest X-ray showed a reduction in tumor size on day 6.**

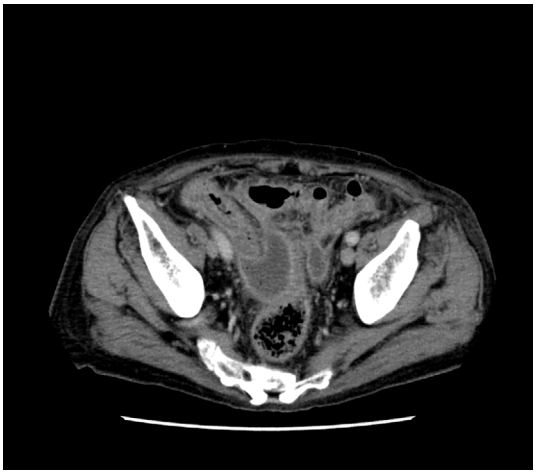

Figure 3. **Abdominal contrast enhanced CT demonstrated a fluid collection indicating an abscess in the lower quadrant.**

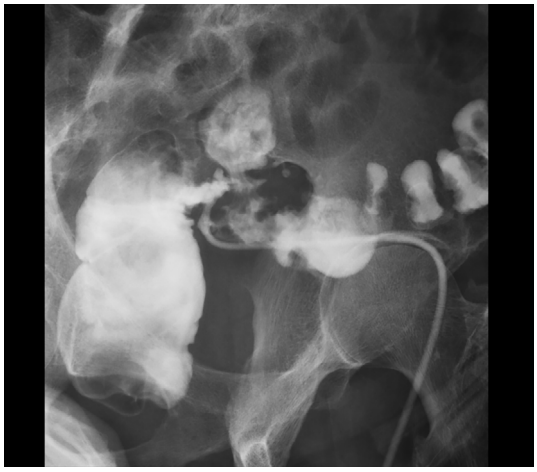

Figure 4. **Fistulography showed a fistula from the rectum to the abscess.**

fatigue and anorexia. EML4-ALK rearrangement was detected from a pleural effusion specimen via a reverse transcription polymerase chain reaction of the cDNA. Crizotinib (250 mg, twice daily) was administered as a second-line treatment. At the time, his height was 152 cm and his body weight was 45.7 kg.

After 6 days of crizotinib, a chest X-ray revealed a reduction in the tumor size (Fig. 2). The patient reported dysgeusia and nausea for the first few days, and then developed fever, vomiting, and diarrhea on day 9. Crizotinib was discontinued on that day. Enterocolitis was considered in the differential diagnosis; ceftriaxone (2 g) was administered based on this consideration. Despite the administration of antibiotics for 3 days, the patient had persistent fever and abdominal pain, and developed rebound tenderness in the right lower abdomen.

Contrast-enhanced abdominal CT showed a low-density area in the abdominal cavity (Fig. 3). A contrast examination confirmed a well-defined abscess cavity following drainage. A 7-Fr pigtail catheter was inserted under ultrasound guidance for longer-term drainage, and treatment with meropenem (1 g, three times a day) was initiated.

Although the abscess gradually decreased in size, a fistula from the rectum to the abscess was detected on fistulography, and a diagnosis of lower intestinal tract perforation with abscess formation was made (Fig. 4). The fistula closed after frequent irrigation and the drainage of the abscess. The patient was discharged without medication, and was followed closely without treatment.

After the discontinuation of crizotinib, the pleural effusion increased and the patient complained of dyspnea on exertion. ALK rearrangement was detected via immunohistochemistry and a fluorescence *in situ* hybridization analysis as routine companion diagnostics. Treatment with alectinib was initiated at a dose of 300 mg, twice daily. The patient's carcinoembryonic antigen (CEA) level decreased, and he remains under treatment as an outpatient at our department. The patient's pleural effusion has not changed and he has not complained of dyspnea.

Discussion

EML4-ALK rearrangement is found in approximately 5% of cases of NSCLC (1). A phase III trial comparing the efficacy and safety of the standard regimen to crizotinib in primary treatment found that crizotinib was associated with significantly longer progression-free survival and a higher objective response rate. The study also reported that crizotinib was generally well tolerated (2), with the most commonly reported adverse events being visual dysfunction, gastrointestinal symptoms including nausea, diarrhea, and vomiting, and edema.

Gastrointestinal perforation (GI) commonly occurs in association with conventional cytotoxic chemotherapy. The pathogenesis of crizotinib-induced GI perforation is incompletely understood; more recently, some reports have described cases of severe GI toxicity (3, 4). In our case, we did not observe metastasis or diverticula on abdominal contrast-enhanced CT, and the intraabdominal abscess resolved with conservative treatment. Because we did not perform a rectal biopsy, we cannot be sure that the rectum was not involved in the metastatic tumor. GI metastasis of lung cancer is rare. Kim et al. (5) reported that GI metastasis only occurred in 0.19% of patients with lung cancer. Although GI metastasis from lung cancer is characterized by acute episodes of abdominal symptoms and a fulminant course, our patient responded to conservative management. Since then, his clinical course has been uneventful.

In our case, crizotinib produced marked tumor regression within a few days. There are two reported cases of EGFR-tyrosine kinase inhibitor (TKI) associated GI perforation without GI metastasis (6, 7). ALK inhibitor has similar characteristics to EGFR TKI, which is known for the rapid onset of its action. Molecularly targeted drug-induced GI perforation may occur independently of tumor necrosis. In the present study, we reported a case of GI perforation that occurred in association with the administration of crizotinib. Tissue fragility due to aging, steroid-induced mucosal damage, crizotinib-induced mucosal damage, increased intraluminal pressure due to hyperperistalsis, and infection, are other risk factors for GI perforation.

The extent of adverse events may be associated with the crizotinib levels in the blood. Kurata et al. (8) reported that the cumulative number of adverse events on day 28 in patients with a higher trough concentration of crizotinib was approximately 3-fold greater than that of patients with a lower trough concentration of crizotinib. Our patient was elderly and his body surface area was smaller than that of the average Japanese man, suggesting that his dose of crizotinib (on a dose to body weight basis) might have led to higher trough and peak levels. Fukuizumi et al. (9) reported a successfully treated case in which a modification of the drug schedule was more effective than dose reduction for avoiding severe adverse events. Given the difficulties associated with crizotinib in our case, determining the dosage based on the body surface area (BSA)-rather than body weight-might have been better for avoiding gastrointestinal adverse events. Alectinib, which shows good tolerability, has clinical activity in patients with acquired resistance to crizotinib tolerability (10). Alectinib can be expected to be widely used in the treatment of EML4-ALK rearrangement-positive NSCLC.

In conclusion, with molecular targeting undergoing rapid approval, genotype-directed therapy for advanced NSCLC may be accompanied by unexpected adverse effects, and requires considerable attention on the part of the treating oncologist.

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

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