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Case Report

Multiple Brain Metastases in a Patient with ROS1 Fusion-Positive Lung Adenocarcinoma as a Disease Flare due to Crizotinib Cessation Caused by Disseminated Aseptic Inflammation from Crizotinib-Associated Renal Cysts: A Case Report

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Lung cancer · Metastasis · Non-small cell lung cancer · Recurrence · Adverse effects · Tyrosine-kinase inhibitor

Abstract
Rapid tumor growth after cessation of molecularly targeted drugs, called "disease flare," may occur and affect the prognosis of lung cancer. However, this phenomenon has never been reported in ROS proto-oncogene 1 (ROS1) fusion-positive lung adenocarcinoma. Herein, we report a disease flare in a patient with ROS1 fusion-positive lung adenocarcinoma. A 60-year-old female was diagnosed with stage IVA ROS1 fusion-positive lung adenocarcinoma via bronchoscopy. Although crizotinib, an ROS1 tyrosine kinase inhibitor, achieved a partial response, a mass lesion appeared in the patient's right kidney 12 months after starting crizotinib, which was diagnosed pathologically as crizotinib-associated renal cysts (CARCs). Given that readministration of crizotinib repeatedly induced CARC-like aseptic inflammation that appeared to be disseminated around surgical site, crizotinib treatment had to be abandoned. Around 25 days after crizotinib cessation, she was referred to the emergency department with a

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convulsive seizure and hemiparesis due to new, rapidly growing brain metastases. Whole-brain irradiation and administration of another ROS1 tyrosine kinase inhibitor, entrectinib, markedly ameliorated the metastases and improved hemiparesis. This has been the first report of a disease flare after crizotinib cessation due to CARCs in a patient with ROS1 fusion-positive lung adenocarcinoma. Attention should be paid to disease flare, especially in the brain, when molecularly targeted medication is stopped due to adverse events in ROS1 fusion-positive lung adenocarcinoma. Switching to drugs that penetrate the blood-brain barrier could overcome disease flare in the brain.

Introduction

ROS proto-oncogene 1 (ROS1) fusion-positive lung adenocarcinoma, first identified in 2007 and further established in 2012, is a rare type of lung cancer accounting for approximately 1% of all lung adenocarcinomas [1–3]. Recent clinical trials have shown that ROS1 tyrosine kinase inhibitors, such as crizotinib and entrectinib, achieved high response rates and long progression-free survival with mild adverse events [4, 5].

However, rapid tumor growth after cessation of molecularly targeted drugs, called "disease flare," may occur, which can cause poor prognosis among affected patients [6]. Most reports have focused on epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors. The frequency of disease flares in EGFR-mutated non-small cell lung cancer varies from 4% to 23% in previous reports [6–8], while only a few cases of disease flares have been reported in lung cancer after discontinuation of molecularly targeted medicines other than EGFR tyrosine kinase inhibitors [9, 10]. Here, we report the first case of ROS1 fusion-positive adenocarcinoma wherein brain metastasis grew rapidly as a disease flare after crizotinib cessation caused by disseminated aseptic inflammation from crizotinib-associated renal cysts (CARCs), an uncontrollable adverse event.

Case Report/Case Presentation

A 60-year-old Japanese female with a history of depression and tuberculosis was referred to our hospital due to a lung nodule in the right lower lobe on computed tomography (CT) upon medical examination. She quit smoking 10 years ago with an 8 pack-year history and no family history of cancer. Imaging examinations revealed pleural dissemination and mediastinal lymph node adenopathy (cT4N2M1a Stage IVA). Endobronchial ultrasound-guided transbronchial needle aspiration of the mediastinal lymph nodes revealed adenocarcinoma. Molecular diagnostics of the tumor sample revealed ROS1 gene rearrangement without EGFR or anaplastic lymphoma kinase gene alteration.

Based on the presence of ROS1 gene rearrangement, oral crizotinib treatment was started. Crizotinib achieved a partial response according to the Response Evaluation Criteria in Solid Tumors version 1.1 and maintained its effectiveness with minimal adverse events.

However, CT 12 months after crizotinib initiation revealed a mass in the upper pole of the right kidney protruding toward perirenal fat (shown in Fig. 1a). Contrast-enhanced CT showed a polycystic mass with enhanced edges and septa. Considering that only a small lesion was detected 4 months prior but not at the time of crizotinib initiation, partial nephrectomy was performed by the Department of Urology to diagnose the mass. Pathology revealed

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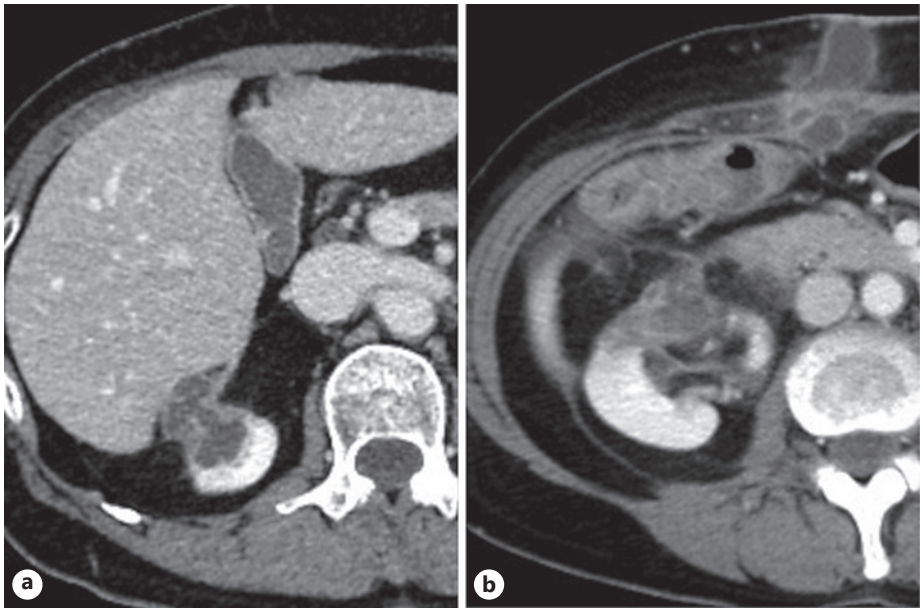

Fig. 1. a Contrast-enhanced computed tomography images showing a mass lesion in the upper pole of right kidney protruding toward the perirenal fat, which was later diagnosed pathologically as crizotinib-associated renal cysts (CARCs). **b** CARC-like aseptic abscesses along the abdominal wall near the surgical wound appeared after the readministration of crizotinib. The figure also shows similar lesions remaining in the resected right kidney.

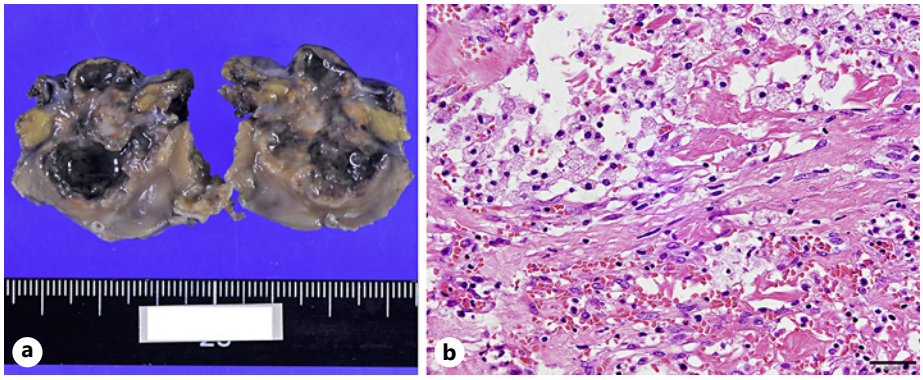

Fig. 2. a Macroscopic findings of the surgical specimen following right partial nephrectomy showing a yellowish-brown mass with fibrosis and cystic degeneration involving perirenal fat. **b** High-power field image with hematoxylin-eosin staining showing xanthogranulomatous inflammation characterized by infiltration of lipid-laden macrophages and other inflammatory cells, fibrosis with hyalinization, and hemosiderin deposition. Scale bar, 20 μm.

xanthogranulomatous inflammation characterized by infiltration of lipid-laden macrophages and other inflammatory cells, fibrosis with hyalinization, and vasculation without malignancy or microbes (shown in Fig. 2a, b), which was consistent with CARCs. The day after surgery, crizotinib was restarted. Twenty-two days after restarting crizotinib, the patient developed fever. Laboratory data revealed elevated C-reactive protein, with subsequent CT showing abscess-like inflammation in the abdominal wall near the surgical wound and around right kidney (shown in Fig. 1b). Considering that antibiotic administration (cefaclor) had no effect,

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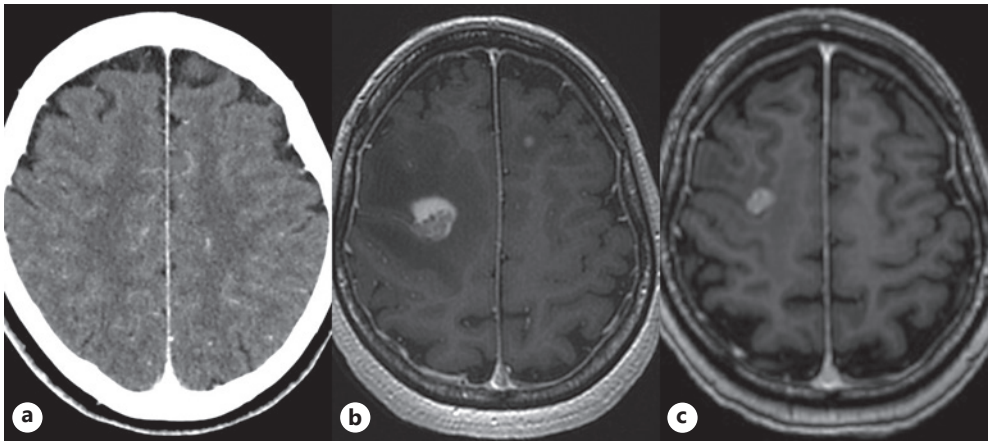

Fig. 3. a Enhanced computed tomography images obtained 26 days before the emergency hospitalization, from which brain metastases were not detected. **b** Enhanced magnetic resonance images on the emergency hospitalization showing a "disease flare" of brain metastases with brain edema. **c** Image of the same lesions obtained 14 days after entrectinib initiation, which regressed remarkably.

crizotinib was stopped and surgical cleaning was performed. No bacteria were detected from the culture of either the swab from the wound before starting antibiotics or the specimen from surgical cleaning, suggesting that these disseminated aseptic lesions were similar to CARCs, although pathological evaluation was not performed in the second surgery.

Given the improved laboratory findings after the second surgery, crizotinib was started again. However, the patient developed fever again, prompting crizotinib to be abandoned. After crizotinib was stopped, C-reactive protein and fever improved spontaneously. CT upon crizotinib cessation showed only a well-controlled primary tumor without any other obvious lesions, including those in the brain.

On day 25 after discontinuation, however, she was referred to the emergency department with a convulsive seizure and right hemiparesis. Enhanced magnetic resonance imaging revealed multiple brain metastases with edema which were not detected from the CT images obtained 26 days before admission (Fig. 3a, b). Thus, the rapid disease progression after crizotinib discontinuation in the current case was considered to be a "disease flare." Anticonvulsive agent (levetiracetam), dexamethasone, concentrated glycerin administration, and whole-brain irradiation (30 Gy/10 fraction) was started. Given that dexamethasone promoted no improvement in right hemiparesis, another ROS1 tyrosine kinase inhibitor with high central nervous system (CNS) penetration [5, 11], entrectinib, was started on day 10 after admission. Hemiparesis improved, with subsequent magnetic resonance imaging on day 14 of entrectinib administration, showing a remarkable regression of the brain metastases with surrounding brain edema (shown in Fig. 3c). As of 3 months after entrectinib treatment, the disease remained well controlled without recurrence of brain lesions.

Discussion/Conclusion

We herein report the first case of a "disease flare" involving brain metastasis in a patient with ROS1 fusion-positive adenocarcinoma after crizotinib cessation due to CARCs. Although disease flares are an uncommon event, most develop after the cessation of EGFR tyrosine kinase inhibitors because of disease progression in EGFR-mutated non-small cell lung cancer. While no clear definition of a disease flare has yet been established, Chaft et al. [7] defined it

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as hospitalization or death attributable to disease progression after stopping tyrosine kinase inhibitors during the 21- to 28-day washout period. Akamatsu et al. [8] speculated that while uncommon, disease flares may occur more frequently in cases not switching their treatment drug for months after Response Evaluation Criteria in Solid Tumors progression. Based on this speculation and given no previous case series on disease flares after discontinuation of a drug due to adverse events, disease flares similar to that in the current case may be even less frequent. The mechanism by which a disease flare develops has yet to be clarified. However, stopping the inhibition of the kinase cascade in sensitive tumor cell clones, which still depend on the cascade, may accelerate tumor growth. In fact, patients with gastrointestinal stromal tumors who were free from progression for 3 years exhibited rapid progression after imatinib discontinuation but then regressed again after resuming imatinib treatment [12]. Given that early dissemination of cancer cells has been known to colonize distant organs at early stages of the disease and survive as micrometastasis for several months to years, possibly even remaining in supportive niches after chemotherapy [13], tumor cells causing the disease flare may have colonized and remained in brain before discontinuing crizotinib in our case. The brain is one of the major sites of disease flare [7], perhaps because the limited CNS penetration of anticancer drugs such as crizotinib facilitates the survival of colonized sensitive clone.

It is also important that CARCs were evaluated pathologically via surgical biopsy in our case and CARC-like inflammation could be disseminated after surgical biopsy. CARCs are uncommon events defined as newly developed or enlarged renal cystic lesions on CT during crizotinib administration, with an incidence rate of 1.2–42% [14–16]. CARCs are complex renal cysts on CT classified as category III or IV according to the Bosniak Renal Cyst Classification System [17], which suggests the difficulty in ruling out the possibility of malignancy on CT. Only a few cases with CARCs have been reported to receive needle biopsy [16], with the current report being the first on cases with CARCs undergoing surgical resection. The pathology of CARCs in our case revealed cystic degeneration caused by xanthogranulomatous inflammation characterized by infiltration of lipid-laden macrophages and other inflammatory cells, fibrosis with hyalinization, vasculation with negative bacterial culture, and no malignant cells such as that in a previous report [16]. Although the mechanism by which CARCs develop remains unknown, studies have speculated the involvement of abnormal lipid metabolism with inflammation in certain cells or tissues based on the pathological findings in our case. A previous study revealed that mice lacking MET proto-oncogene (MET) exhibited severe fatty liver degeneration with increased inflammation of immune cells, causing nonalcoholic steatohepatitis [18]. Evidence suggests that MET inhibition by crizotinib might generate CARCs, although it is difficult to rule out the ability of other MET inhibitors to cause CARC-like complications in clinical studies. Although some reports have reported the spontaneous regression of CARCs during continued crizotinib treatment, the inflammation can occasionally spread outside the kidney, which requires discontinuation of crizotinib [16]. Moreover, we note that CARC-like lesions had spread around the wound after surgical biopsy in our case, suggesting that a disseminated fragment of CARC lesions may also induce inflammation and that surgical biopsy should be discouraged when CARCs are suspected.

Based on our experience with the current case, attention should be paid to disease flare, especially in the brain, when molecularly targeted medication is stopped due to adverse events in ROS1 fusion-positive lung adenocarcinoma. Given the current approval of another ROS1 inhibitor with high CNS penetration, entrectinib, for ROS1-positive non-small cell lung cancer, when crizotinib needs to be discontinued due to adverse events, such as uncontrollable CARCs without disease progression, switching to entrectinib might be a preferred option instead of cessation of crizotinib.

Statement of Ethics

This study protocol was reviewed and approved by the Institutional Ethical Board at the University of Tokyo, approval number 2739-(10). Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Yosuke Amano was a major contributor in writing the manuscript. Hidenori Kage helped draft the manuscript. Yosuke Amano, Hidenori Kage, Goh Tanaka, and Takahide Nagase were involved in the patient management. Yusuke Sato performed the surgical operation. Mariko Tanaka performed the histological examination and provided pathological implication. Yosuke Amano, Hidenori Kage, Goh Tanaka, Yusuke Sato, Mariko Tanaka, and Takahide Nagase read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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