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【 CASE REPORT 】

Successful Treatment with Low-dose Crizotinib in a Patient with *ROS1*-rearranged Lung Cancer Who Developed Crizotinib-induced Heart Failure

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Abstract:
Crizotinib shows antitumor activity against *C-ros oncogene 1*-rearranged non-small-cell lung cancer (NSCLC). While corrected QT interval (QTc) prolongation and bradycardia are known as cardiac adverse effects, little is known about crizotinib-related heart failure. Our patient with *C-ros oncogene 1*-rearranged NSCLC on a reduced dose of crizotinib (200 mg twice daily) after initially experiencing bradycardia and QTc prolongation developed crizotinib-induced heart failure. With further dose reduction (250 mg once daily), there was no recurrence of any cardiac adverse effects, and the patient achieved a long-term response. Although crizotinib can cause heart failure, continuation of crizotinib at a low dose may be an effective treatment option.

Key words: *ROS1*-rearrangement, crizotinib, cardiotoxicity, heart failure, QTc prolongation

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Introduction

C-ros oncogene 1 (*ROS1*) rearrangements are identified in approximately 1-2% of non-small-cell lung cancers (NSCLCs) (1). Crizotinib is an oral, small-molecule tyrosine kinase inhibitor of anaplastic lymphoma kinase (ALK), mesenchymal-epithelial transition/hepatocyte growth factor receptor (MET), and *ROS1* kinases. It has considerable antitumor activity against *ROS1*-rearranged NSCLC (2, 3). Common treatment-associated adverse events include visual disorders, nausea, diarrhea, and transaminase elevation (2, 3). With the increasing administration of crizotinib, cardiotoxic adverse events, such as corrected QT interval (QTc) prolongation and bradycardia, have also been reported occasionally (4). However, little is known about crizotinib-related heart failure, and its management has not been well-established (5).

We herein report a patient with *ROS1*-rearranged NSCLC who developed crizotinib-induced heart failure and recovered with a temporary interruption of the drug, achieving a long-term response with a reduced dosage of the tyrosine kinase inhibitor.

Case Report

An 80-year-old woman presented to us with a 2-month history of persistent cough. Chest computed tomography (CT) revealed a pulmonary mass and mediastinal lymphadenopathy. After a transbronchial biopsy, she was diagnosed with *ROS1*-rearranged adenocarcinoma of the lung. Fluorine 18-labeled fluorodeoxyglucose positron emission tomography-computed tomography (FDG PET-CT) showed liver metastases, so the patient was diagnosed with stage IVB disease (cT2N2M1c). Concurrent conditions included hypertension and hyperlipidemia, without any cardiovascular disease. She was prescribed telmisartan 40 mg and rosuvastatin 2.5 mg once daily. An electrocardiogram performed before treatment showed a pulse rate of 72 bpm and a QTc of 401 ms.

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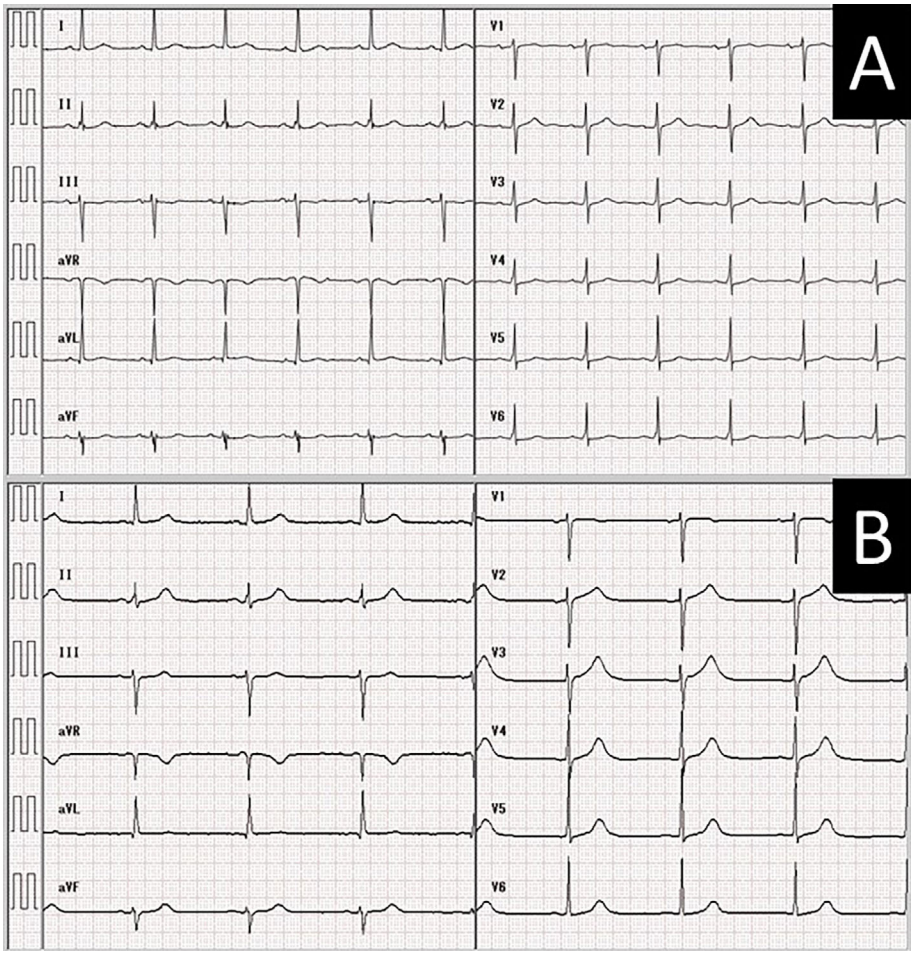

Figure 1. Electrocardiogram findings before and after crizotinib administration. The electrocardiogram before crizotinib treatment was within normal limits (A). The electrocardiogram on day 8 of crizotinib treatment shows sinus bradycardia (heart rate 47 bpm) and QTc prolongation (QTc 517 ms) (B). QTc: corrected QT interval

The patient was then prescribed oral crizotinib 250 mg twice daily as a first-line treatment for the lung cancer. On day 8 of crizotinib therapy, she developed asymptomatic sinus bradycardia (heart rate, 47 bpm, grade 2 according to Common Terminology Criteria for Adverse Events, version 5.0) and QTc prolongation (QTc, 517 ms, grade 3) (Fig. 1). On withholding the drug for 3 days, her heart rate recovered to 60 bpm, and the QTc interval improved to 408 ms. Thereafter, treatment with crizotinib was resumed at a reduced dose of 200 mg twice daily.

On day 7 of the reduced crizotinib dose, the patient developed chest discomfort, leading to respiratory failure (heart rate 62 bpm, blood pressure 120/58 mmHg, SpO_2 89% in ambient air). Chest X-ray and chest CT revealed cardiac enlargement, bilateral pleural effusion, and pulmonary congestion (Fig. 2). The B-type natriuretic peptide (BNP) level was as high as 194 pg/mL. Although echocardiography showed a preserved left ventricular ejection fraction of 68.9%, the average mitral E/e' ratio was 17.4, septal e' velocity was 5.7 cm/s, TR velocity was 2.77 m/s, and LA volume index was 43.6 mL/m^2, which met the diagnostic criteria of heart failure with a preserved ejection fraction (HFpEF) of the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations (6). There was no bradycardia or QT prolongation at this time, the troponin I level was normal, and there was no ischemic heart disease or valvular heart disease that could cause heart failure. She was not receiving any new medications other than crizotinib, telmisartan and rosuvastatin. Based on these findings, the patient was diagnosed with crizotinib-related heart failure (grade 3).

Crizotinib therapy was again interrupted, and the patient was administered furosemide 20 mg per day. After 7 days of this treatment, the patient recovered from her heart failure. We resumed crizotinib at a further reduced dose of 250 mg once daily. No recurrence of heart failure, bradycardia, or QTc prolongation was observed in the patient with this low-dose regimen. Thereafter, tumor shrinkage was observed, and the patient achieved a partial response (PR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. She maintained this PR to crizotinib at the same dose for 31 months.

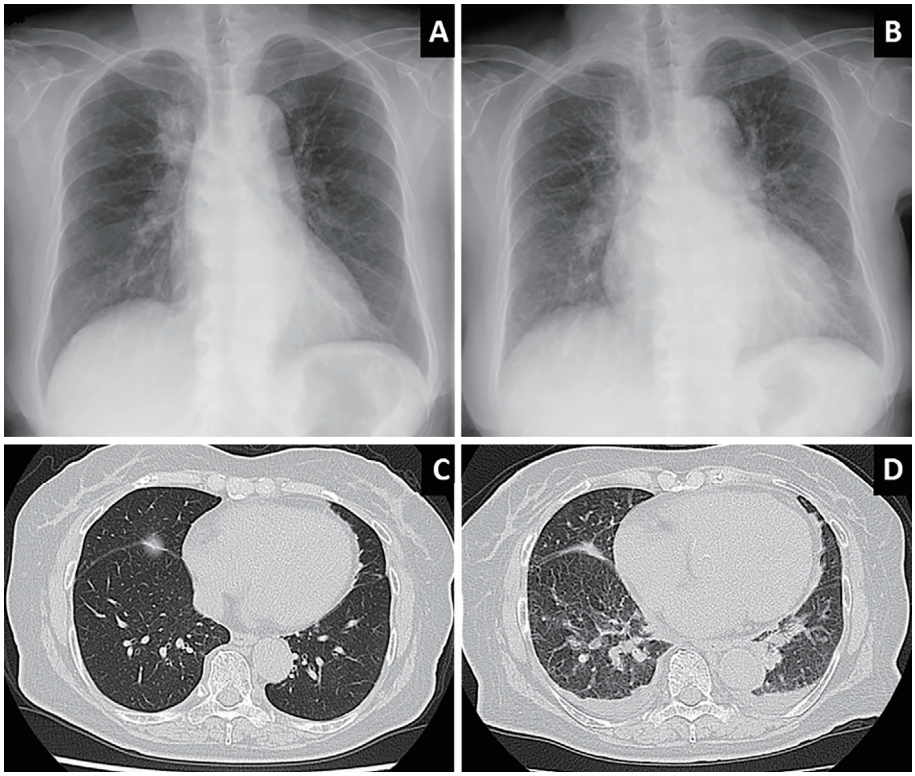

Figure 2. **Chest X-ray and computed tomography (CT) findings. Chest X-ray and CT findings before crizotinib therapy (A, C). Cardiac enlargement, bilateral pleural effusion, and pulmonary congestion seen after seven days of treatment with a reduced dose of crizotinib (B, D).**

Discussion

Our experience with this patient highlights the possibility of crizotinib-induced heart failure in patients with *ROS1*-rearranged NSCLC. It also indicates that affected patients may be able to continue treatment at a reduced dose and experience therapeutic benefit.

First, this case demonstrates that crizotinib treatment can lead to heart failure along with causing bradycardia and QTc prolongation. Sinus bradycardia and QTc prolongation are known adverse cardiac effects of crizotinib, with previously reported incidences of 10.1% and 3.2%, respectively (2, 3, 5). These adverse events are asymptomatic in most patients and rarely lead to the discontinuation of crizotinib. In contrast, crizotinib-induced heart failure is rare, with only a few case reports of ALK-rearranged NSCLC (7, 8). In a report of cardiotoxicity with targeted therapy for NSCLC, crizotinib significantly increased the risk of conduction disturbance and QTc prolongation compared with other targeted therapies, but there was no apparent increase in the risk of heart failure (9).

Although various tyrosine kinase inhibitors (TKIs), including crizotinib, are known to cause cardiotoxicity, the mechanism by which TKIs cause cardiac damage is not well understood. TKI-induced cardiotoxicity is considered to result from the disturbance of tyrosine kinase activity in cardiomyocytes. Many pathways associated with tumor proliferation are also important for maintaining cardiomyocytes. ERBB2 in cardiomyocytes is a co-receptor in the cardiomyocyte survival pathway; dysregulation of the downstream pathway of PI3K-AKT has been shown to induce ischemic heart disease and heart failure, while RAF is one of the important components of pro-survival signaling linked to heart disease (10). These mechanisms, in addition to the increased cardiovascular risk and impaired drug metabolism due to the advanced age, may have contributed to the development of heart failure in our patient.

Second, reducing the dose of crizotinib in our patient with *ROS1*-rearranged NSCLC after her recovery from heart failure allowed treatment continuation and resulted in a long-term response. Heart failure is sometimes serious and can impair the patient's quality of life or affect subsequent anticancer therapy. Whether or not crizotinib administration can be continued in affected patients is not clear. While temporary suspension and re-administration of crizotinib at a reduced dose are recommended for drug-induced bradycardia and QTc prolongation, the management of crizotinib-induced heart failure is not well-established (5). Heart failure induced by molecular-targeted drugs, such as trastuzumab and lapatinib, for other cancers is not related to the cumulative dose and is generally reversible (11). Trastuzumab-induced cardiac dysfunction has been observed to subside within six months in most patients, and re-exposure to trastuzumab after recovery from cardiac dysfunction is generally well tolerated (11). Osimertinib, a key treatment drug for

epidermal growth factor receptor (EGFR)-mutated NSCLC, is known to cause the adverse event of a decreased ejection fraction of the heart, which is reportedly reversible (12).

In *ROS1*-rearranged NSCLC, crizotinib shows long-term efficacy, and the progression-free survival (PFS) of patients in a clinical trial setting was 19.2 months (2). Therefore, the continuation of crizotinib in our patient offered the possibility of a substantial long-term PFS. While the crizotinib dose had already been lowered due to QTc prolongation, we decided to continue the drug at a further reduced dose after the patient recovered from cardiac failure. This resulted in a long-term response without exacerbation of the failure. EGFR-TKIs for EGFR-mutated lung cancer have demonstrated no significant difference in the survival of patients who received a dose reduction due to toxicity compared with those who did not require a dose reduction (13, 14). Our experience suggests that NSCLC patients with heart failure caused by crizotinib may continue the drug at a reduced dosage and still derive therapeutic benefit.

Conclusion

Cardiotoxicity is one of the concerning adverse events related to crizotinib administration. In addition to bradycardia and QTc prolongation, drug-induced heart failure may occur during treatment. Re-administration of crizotinib at a reduced dose in affected patients may allow for treatment continuation, which can elicit a long-term therapeutic response.

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

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