CASE REPORT

Reoccurrence of takotsubo cardiomyopathy induced by osimertinib: A case report

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1 | INTRODUCTION

Chemotherapy-induced Takotsubo (stress) cardiomyopathy (TC) has been reported for several anticancer agents including antimetabolites, fluoropyrimidines, and molecularly targeted agents.1 Some molecularly targeted agents reportedly cause cardiovascular side effects, including heart failure, arrhythmia (QT prolongation), and myocardial infarction.2 The epidermal growth factor receptor (EGFR) inhibitors except trastuzumab are known to cause less cardiotoxicity than BCR-ABL inhibitors and vascular endothelial growth factor (VEGFR) inhibitors.3 However, osimertinib has been reported more adverse cardiac events than other EGFR inhibitors, including heart failure.4–6 While there exist a few reports of osimertinib-induced heart failure in detail, reporting nonspecific cardiomyopathy,6 none have so far reported TC induced by osimertinib. Herein, we report a case of TC caused by osimertinib.

2 | CASE HISTORY

A 73-year-old woman with no history of smoking underwent a thoracoscopic right upper-middle lobectomy in 2016 for non-small-cell lung cancer (NSCLC). Her clinical stage was T2N0M0, and she did not receive adjuvant chemotherapy. One year later, a chest computed tomography (CT) scan showed pleural dissemination, and brain metastasis was suspected based on brain magnetic resonance imaging (MRI). She was admitted to our institution for targeted therapy. One year and 10 months after administering erlotinib and bevacizumab as first-line therapy (a total of 26 courses), pleural dissemination was found to be a progressive disease. Pleural biopsy revealed a T790M mutation.

Osimertinib (80mg/day, taken orally) was chosen as second-line therapy. Within 1 month of starting osimertinib, she was admitted to our institution with progressive shortness of breath, fatigue, and edema in the body and extremities. Chest radiography revealed pulmonary congestion, pleural effusion, and cardiac dilation. An echocardiogram revealed left ventricular akinesis from the apical to the midventricular portion, which did not match with coronary arterial perfusion (Figure 1A,B). The left ventricular dimension increased from 34 mm preosimertinib treatment to 46 mm, and left ventricular ejection fraction (LVEF) was reduced from 75% to 58% (Table 1). The electrocardiogram changed from normal to a right bundle branch block, and QTc(F) interval changed from 428 ms to 487 ms (Figure 2A,B). She was diagnosed as symptomatic...
acute heart failure. The daily medications were olmesartan 20 mg, ursodeoxycholic acid 600 mg, clostridium butyricum combined drug 3 g, esomeprazole 20 mg, sucralfate 30 ml, and tramadol 75 mg.

3 | **DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of cause of heart failure included coronary artery disease, arrhythmia, and valvular disease. Cardiac MRI showed no significant stenosis of the coronary arteries, and a monitored electrocardiogram showed no bradycardia nor tachycardiac arrhythmia. Echocardiography revealed no significant left-side valvular disease.

4 | **OUTCOME AND FOLLOW-UP**

She was diagnosed with osimertinib-induced acute heart failure due to TC. She was admitted to our institution on the same day for the treatment of cardiac failure. Her condition improved after discontinuing osimertinib and adding treatment for heart failure including spironolactone 25 mg and bisoprolol 1.25 mg.

Thirty-five days after admission, left ventricular wall motion abnormality improved to almost normal kinesis (Table 1, Figure 1C,D), and electrocardiogram showed ST changes normalized after extensive negative T waves and QT prolongation (Figure 2C,D). She improved from Class IV to Class II as per the New York Heart Association Classification.
Since osimertinib was highly effective against her own lung cancer, the treatment was restarted at a reduced dose of 40 mg/day as outpatient care. After 63 days of restarted osimertinib therapy, an echocardiogram showed hypokinesis on the left ventricular apical portion (Table 1, Figure 1E,F). Electrocardiogram showed reappearance of extensive negative T waves and QT prolongation (Figure 2E). She was diagnosed with asymptomatic TC, and osimertinib treatment was subsequently stopped. No new cardiotoxic agents were added for her. Two weeks after stopping osimertinib, left ventricular wall motion improved to normal. She was started on third-line chemotherapy.

TC is a transient systolic left ventricular dysfunction with a variety of wall motion abnormalities. Elderly women and emotional or physical triggers were considered to be the cause of TC, but conditions without an evident trigger have also been reported. In a previous study, EGFR was found to be expressed in the central nervous system, and infusion of EGFR into the midbrain had increased dopamine precursor levels in an experimental rat model. One of the mechanisms of osimertinib-induced TC might be that osimertinib may cross the blood–brain barrier, increasing the dopamine release in the central nervous system. Another possible mechanism is that osimertinib inhibits human EGFR2 and cardiomyocyte signaling leading to cause cardiac dysfunction, which is similar to trastuzumab.

Osimertinib may cause TC, which has the possibility of cause of heart failure. The findings of our case study suggest that osimertinib therapy should not be resumed in patients diagnosed with symptomatic heart failure due to TC induced by osimertinib.

### DISCUSSION

Osimertinib is a third-generation oral EGFR tyrosine kinase inhibitor (TKI) used for the treatment of advanced EGFR-mutant NSCLC with acquired T790M mutations. It has also been shown to improve progression-free survival compared with platinum therapy. Although cardiotoxicity from EGFR-TKI (human EGFR1: HER1) has been reported to be less than that of HER2, BCR-ABL, and VEGFR inhibitors, osimertinib is likely to cause cardiac side effects.

#### TABLE 1  Echocardiographic parameters, BNP values, and Number of Figure of echocardiogram and electrocardiogram from baseline to TC treatment

|                          | Baseline | AHF due to TC after osimertinib | After discontinuing osimertinib | After restarting half-dose osimertinib |
|--------------------------|----------|---------------------------------|---------------------------------|---------------------------------------|
| LVDd (mm)                | 34       | 46                              | 43                              | 38                                    |
| LVDs (mm)                | 19       | 30                              | 28                              | 21                                    |
| FS (%)                   | 43       | 36                              | 35                              | 44                                    |
| LVEF (%)                 | 75       | 58                              | 61                              | 64                                    |
| E wave (m/s)             | 0.5      | 0.8                             | 0.8                             | 0.6                                   |
| A wave (m/s)             | 0.6      | 1.0                             | 0.8                             | 0.7                                   |
| E/A ratio                | 0.9      | 0.8                             | 1.0                             | 0.7                                   |
| TR velocity (m/s)        | 2.8      | 3.4                             | 3.1                             | 2.3                                   |
| TR-PG (mmHg)             | 31       | 47                              | 39                              | 22                                    |
| Medial e' (cm/s)         | 3.5      | 3.8                             | 4.0                             | 3.3                                   |
| E/e'                     | 14       | 21.3                            | 20.3                            | 16.8                                  |
| GLS (%)                  | –        | 13.8                            | 16.6                            |                                       |
| BNP (pg/ml)              | –        | 1002.1                          | 63.8                            | 201.2                                 |
| Number of Figure         | –        | Figure 1A,B                     | Figure 1C,D                     | Figure 1E,F                           |
| Number of Figure         | Figure 2A| Figure 2B                       | Figure 2C,D                     | Figure 2E                             |

**Abbrivations:** AHF, acute heart failure; C, Takotsubo (stress) cardiomyopathy; FS, fractional shortening; GLS, global longitudinal strain using speckle tracking method; LVDd, left ventricular diastolic dimension; LVDs, left ventricular systolic dimension; LVEF, left ventricular ejection fraction; PG, pressure gradient; TR, tricuspid regurgitation.
FIGURE 2 Electrocardiogram on baseline (A), on acute heart failure (B), after heart failure treatment (C, D), and on reoccurrence of TC (E). (A). Baseline electrocardiogram was normal sinus rhythm with heart rate of 71 bpm and QTc(F) interval of 428 ms. (B). On acute heart failure due to TC, an electrocardiogram showed complete right bundle branch block with heart rate of 92 bpm and QTc(F) interval of 487 ms. (C). Eleven days after treatment of heart failure, negative T-wave with broad induction was observed. QTc(F) interval was further extended to 551 ms. (D). Nine weeks after treatment of heart failure, ST changes have normalized. QTc(F) interval was shortened to 479 ms. Sixty-three days after restarting osimertinib, negative T-wave with broad induction was observed. QTc(F) was extended to 520 ms

ACKNOWLEDGMENT
None.

CONFLICT OF INTEREST
None declared.

DATA AVAILABILITY STATEMENT
All data that support the findings of this study, which were taken from case clinical records, are available on request from the corresponding author.
CONSENT
Written informed consent was obtained from the patient to publish this report in accordance with the journal’s patient consent policy.

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