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Case Report

Onset of takotsubo syndrome induced by osimertinib in a patient with lung adenocarcinoma

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ABSTRACT

The cardiotoxicity of osimertinib, an epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor, has been recently reported when treating EGFR mutation-positive non-small cell lung cancer. In this report, we describe a case of an 81-year-old female patient diagnosed with Takotsubo syndrome (TTS). TTS occurred despite the patient receiving osimertinib retreatment at reduced doses and having no history of cardiac or respiratory disease. The findings of this case suggest that clinicians should consider the possibility of TTS induced by osimertinib.

1. Introduction

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) are the standard treatment for EGFR mutation-positive non-small cell lung cancer (NSCLC). Osimertinib, a third-generation EGFR-TKI, improves outcomes in patients with EGFR T790M-positive NSCLC and is the first-line treatment for EGFR-mutated NSCLC [1,2]. In clinical trials, osimertinib has been associated with higher rates of adverse cardiac effects, especially QT prolongation, compared with standard EGFR-TKIs, such as gefitinib and erlotinib [2]. Additionally, osimertinib-induced cardiotoxicity has been reported [3].

Takotsubo syndrome (TTS), also known as broken heart syndrome, is a transient left ventricular dysfunction typically triggered by physical or emotional stress. Osimertinib-induced TTS is extremely rare, and only one case has been reported in a patient with recurrent NSCLC with a history of thoracic surgery for primary lung cancer [4].

In this report, we describe a case of osimertinib-associated TTS, despite the patient receiving reduced osimertinib doses and having no history of cardiac or respiratory disease.

2. Case presentation

An 81-year-old female patient presented to our hospital with dyspnea on exertion for 3 weeks. The patient had no history of smoking and respiratory or cardiac disease. Chest computed tomography revealed right-sided pleural effusion and a mass lesion in the right upper lung (Fig. 1). After thoracentesis, transbronchial biopsy, and cranial magnetic resonance imaging, the patient was diagnosed with EGFR mutation-positive lung adenocarcinoma, cT2bN2M1b, Stage IVA, according to the Union for International Cancer Control, 8th edition.

Chest tube drainage and pleurodesis were performed, and the patient was treated with 80 mg/d osimertinib. After 2 weeks of treatment, the patient developed pruritus, and osimertinib treatment was discontinued. Pruritus was resolved with a histamine blocker and topical corticosteroid. Osimertinib treatment was restarted after 4 weeks at a dose of 40 mg/d. The brain natriuretic peptide levels (17.6 pg/mL) and echocardiography, with a left ventricular ejection fraction (LVEF) of 65 %, were normal when osimer-

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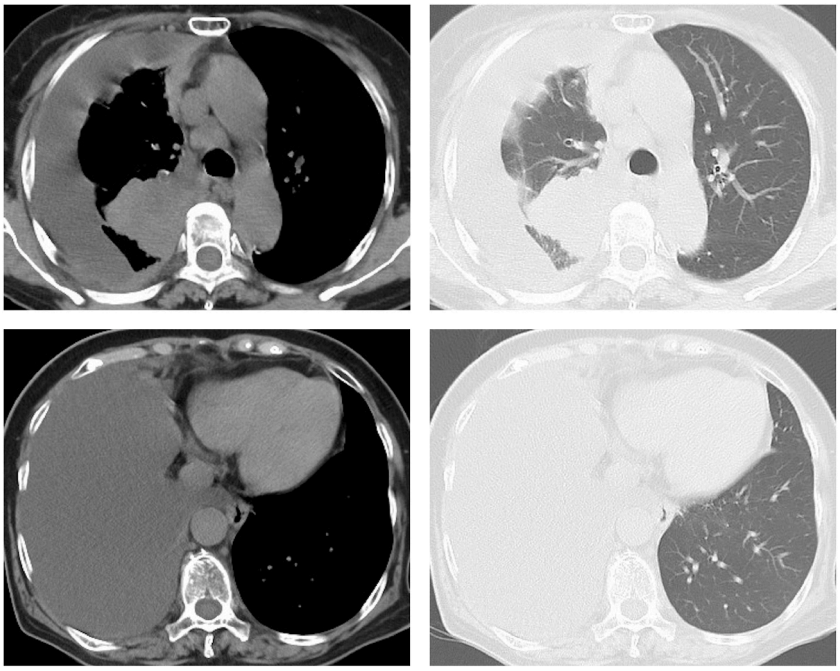

Fig. 1. Chest computed tomography revealing right-sided pleural effusion and a mass in the right upper lung.

tinib was restarted. Although pruritus relapsed, the patient continued osimertinib along with a histamine blocker, achieving a partial response according to the Response Evaluation Criteria in Solid Tumors 1.1.

Six weeks after restarting osimertinib treatment, the patient was admitted because of sudden chest pain after defecation and persistent chest tightness. The creatine kinase MB levels were within normal limits; however, the qualitative troponin T rapid test result was positive. Electrocardiography showed ST segment elevation in the V3-6 leads (Fig. 2A). Echocardiography revealed akinesis of the left ventricular apical segment and left ventricular systolic dysfunction with an LVEF of 41 %. Left ventriculography demonstrated apical akinesis, basal hypercontraction, and no significant coronary artery stenosis (Fig. 2B and C). The patient was diagnosed with acute heart failure due to TTS, and osimertinib treatment was discontinued. Her chest tightness improved the next day, and electrocardiography showed negative T waves in the V1-6 leads (Fig. 3).

Two weeks after TTS onset, gefitinib treatment (250 mg/d) was started as a second-line therapy because the pleural dissemination of lung cancer spread rapidly. The LVEF improved slightly from 41 % to 45 %, and apical akinesis persisted. Gefitinib was effective in stopping disease progression; however, the patient experienced severe glossitis, resulting in the discontinuation of gefitinib after 3 weeks. The patient's general condition gradually deteriorated, and she died after 7 weeks. The negative T waves in the V1-6 leads disappeared on the electrocardiogram taken a week before death, and echocardiography showed normalization of wall motion abnormalities and LVEF.

3. Discussion

The patient had TTS despite receiving a reduced dose of osimertinib for lung adenocarcinoma. No underlying conditions, including cardiac disease, may have affected the onset of TTS.

TTS is a clinical entity characterized by sudden transient left ventricular apical akinesis not associated with obstructive coronary artery disease [5]. It typically manifests in postmenopausal females due to presence of physical or emotional stress [6]. Respiratory disorders have been identified as a physical trigger for TTS [7], and acute respiratory triggers, such as exacerbation of chronic obstructive lung disease and respiratory tract infection, are observed in 7 % of patients with TTS [8]. A systematic review of observational studies describing the association between respiratory disease and TTS revealed that among the TTS cases accompanied by respiratory disease, 39.8 % had obstructive lung disease, 38.9 % had pneumonia, 11.1 % had pulmonary embolism, and 10.2 % had lung cancer [9]. Out of the 11 patients, 7 (63.6 %) patients with lung cancer and TTS were females, and all of them had NSCLC [9]. Notably, the in-hospital mortality rate of patients with lung cancer and TTS was 20 %, which was higher than that of patients with all types of TTS [9].

As the first-line treatment for EGFR mutation-positive NSCLC, osimertinib results in better outcomes compared with standard EGFR-TKIs [2]. Although osimertinib use is associated with lower rates of adverse events that are grade 3 or higher than treatment with standard EGFR-TKIs such as gefitinib and erlotinib, adverse cardiac effects, especially QT prolongation, have been reported to be more frequent in the osimertinib group than in the standard EGFR-TKI group [2].

In a systematic review of case reports and a series describing EGFR-TKI-induced heart failure in NSCLC, osimertinib was administered in 82.6 % of the cases [10], implying that heart failure due to osimertinib is more likely to develop than heart failure due to

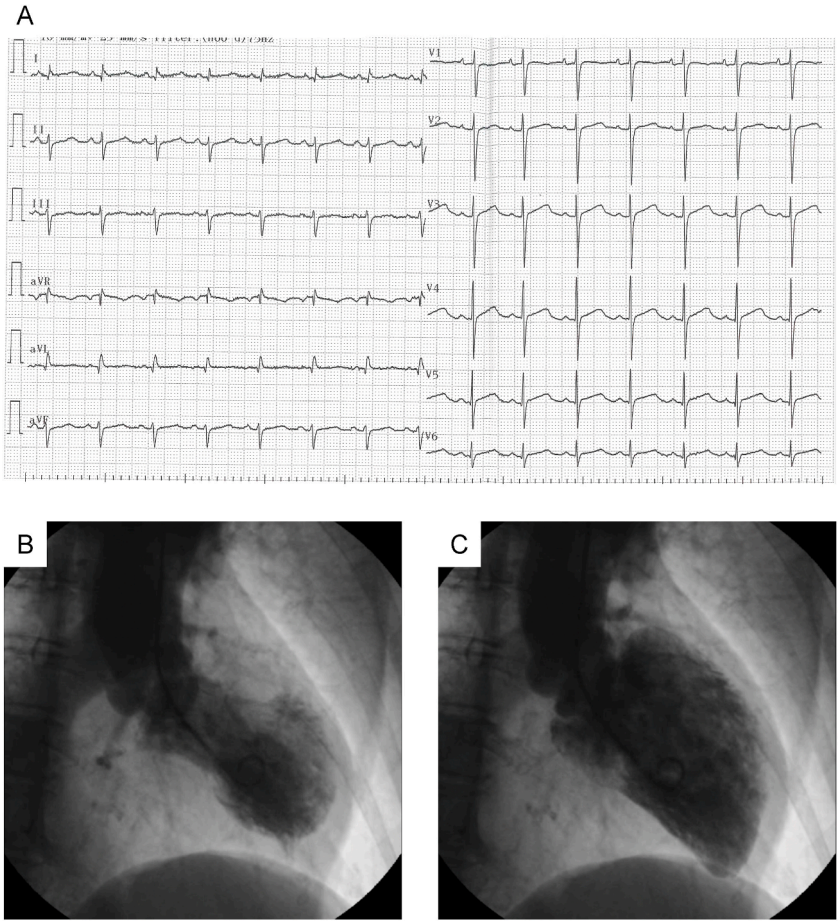

Fig. 2. Electrocardiogram on admission (A) showing ST segment elevation in the V3-6 leads. Left ventriculography during systole (B) and diastole (C) demonstrate apical akinesis and a hypercontractile base.

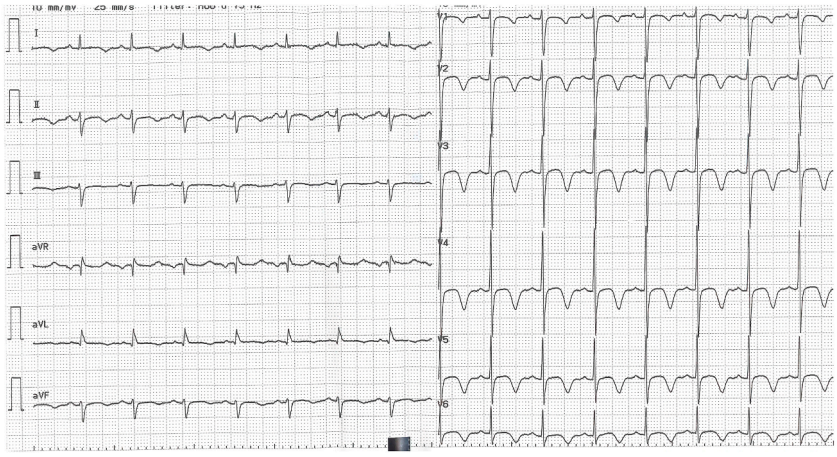

Fig. 3. Electrocardiogram on the second day of admission showing T waves inversion in the V1-6 leads.

other EGFR-TKIs (afatinib, erlotinib, and gefitinib). Moreover, the frequency of osimertinib-induced cardiotoxicity is higher than that of other EGFR-TKIs.

According to the U.S. Food and Drug Administration Adverse Events Reporting System, a pharmacovigilance database, the reporting odds ratios for cardiac failure, atrial fibrillation, and QT prolongation were significantly higher with osimertinib than with other EGFR-TKIs, such as afatinib, erlotinib, and gefitinib [3]. However, no cases of osimertinib-associated TTS have been reported until 2022 [4,11].

Fukuda et al. were the first to report a case of osimertinib-induced TTS in an 81-year-old female with recurrent NSCLC after undergoing a right upper-middle lobectomy. The patient developed acute cardiac failure due to TTS within a month of starting osimertinib treatment [4]. TTS recurred even when a reduced dose of osimertinib was administered. A case series regarding cardiomyopathy-associated osimertinib reported that 2 of 17 patients with EGFR mutation-positive NSCLC had TTS [11]; however, other details have not yet been described. Among the patients with osimertinib-associated cardiomyopathy, approximately 60 % had at least three cardiac risk factors [11]. The top three most common comorbidities were hypertension (88.2 %), dyslipidemia (58.8 %), and atrial fibrillation (47.1 %). The LVEF decreased by a median of 22 % during a median (first quartile-third quartile) of 4.2 months (3.3–9.4 months) in these patients [11].

Our patient had neither a cardiac risk factor nor a history of pulmonary lobectomy and showed normal heart function before restarting osimertinib. Nonetheless, our patient developed TTS after only 6 weeks of dose-dependent treatment. Therefore, patients receiving osimertinib are recommended to undergo early and regular echocardiography to evaluate LVEF and the presence of abnormal wall motion.

Notably, the mechanisms underlying osimertinib-induced cardiotoxicity remain unclear. Osimertinib and its active circulating metabolite AZ5104 inhibit both EGFR and human epidermal growth factor receptor 2 (HER2) *in vitro* [12]. Anti-HER2-targeted therapy is known to cause cardiac toxicity, and inhibition of HER2 by osimertinib and AZ5104 might be associated with cardiotoxicity [13]. β_1-adrenergic receptor-mediated EGFR transactivation has been demonstrated to play a cardioprotective role *in vivo* under conditions of catecholamine excess [14].

4. Conclusion

Clinicians should consider the possibility of osimertinib-induced TTS in patients with EGFR mutation-positive NSCLC, even in the absence of cardiac risk factors or underlying cardiac diseases.

CRediT authorship contribution statement

Shouichi Okamoto: Writing – original draft, Formal analysis, Data curation, Conceptualization. **Mariko Shinomiya:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] T.S. Mok, Y.-L. Wu, M.-J. Ahn, et al., Osimertinib or platinum-pemetrexed in EGFR T790M-positive lung cancer, N. Engl. J. Med. 376 (2017) 629–640, https://doi.org/10.1056/NEJMoa1612674.
[2] J.C. Soria, Y. Ohe, J. Vansteenkiste, et al., Osimertinib in untreated *EGFR*-mutated advanced non-small-cell lung cancer, N. Engl. J. Med. 378 (2018) 113–125, https://doi.org/10.1056/NEJMoa1713137.
[3] K. Anand, J. Ensor, B. Trachtenberg, E.H. Bernicker, Osimertinib-induced cardiotoxicity: a retrospective review of the FDA adverse events reporting System (FAERS), JACC Cardiooncol 1 (2019) 172–178, https://doi.org/10.1016/j.jaccao.2019.10.006.
[4] Y. Fukuda, Y. Kawa, A. Nonaka, H. Shiotani, Reoccurrence of takotsubo cardiomyopathy induced by osimertinib: a case report, Clin. Case Rep. 10 (2022) e6279, https://doi.org/10.1002/ccr3.6279.
[5] J.R. Ghadri, I.S. Wittstein, A. Prasad, et al., International expert consensus document on takotsubo syndrome (Part I): clinical characteristics, diagnostic Criteria, and pathophysiology, Eur. Heart J. 39 (2018) 2032–2046, https://doi.org/10.1093/eurheartj/ehy076.
[6] E. Natale, R. Mistrulli, Takotsubo syndrome: more frequent in women, more dangerous in men, Eur. Heart J. Suppl. 25 Supplement B (2023) B119–B122, https://doi.org/10.1093/eurheartjsupp/suad089.
[7] R. Manfredini, F. Fabbian, A.D. Giorgi, et al., Heart and lung, a dangerous liaison-Tako-tsubo cardiomyopathy and respiratory diseases: a systematic review, World J. Cardiol. 6 (2014) 338–344, https://doi.org/10.4330/wjc.v6.i5.338.
[8] K. Kato, V.L. Cammann, L.C. Napp, et al., Prognostic impact of acute pulmonary triggers in patients with takotsubo syndrome: new insights from the International takotsubo Registry, ESC Heart Fail 8 (2021) 1924–1932, https://doi.org/10.1002/ehf2.13165.
[9] P. Li, Y. Wang, J. Liang, et al., Takotsubo syndrome and respiratory diseases: a systematic review, Eur. Heart J. Open 2 (2022) oeac009, https://doi.org/10.1093/ehjopen/oeac009.
[10] M.N. AlShatnawi, R.A. Shawashreh, M.A. Sunoqrot, A.R. Yaghi, A systematic review of epidermal growth factor receptor tyrosine kinase inhibitor-induced heart failure and its management, Egypt, J. Intern. Med. 34 (2022) 85, https://doi.org/10.1186/s43162-022-00176-y.
[11] M.J. Franquiz, S. Waliany, A.Y. Xu, et al., Osimertinib-associated cardiomyopathy in patients with non-small cell lung cancer: a case series, JACC Cardiooncol 5 (2023) 839–841, https://doi.org/10.1016/j.jaccao.2023.07.006.
[12] D.A. Cross, S.E. Ashton, S. Ghiorghiu, et al., AZD9291, an irreversible EGFR TKI, overcomes T790M-mediated resistance to EGFR inhibitors in lung cancer, Cancer Discov. 4 (2014) 1046–1061, https://doi.org/10.1158/2159-8290.CD-14-0337.
[13] G.A. Viani, S.L. Afonso, E.J. Stefano, L.I. De Fendi, F.V. Soares, Adjuvant trastuzumab in the treatment of her-2-positive early breast cancer: a meta-analysis of published randomized trials, BMC Cancer 7 (2007) 153, https://doi.org/10.1186/1471-2407-7-153.
[14] G. Kallifatidis, D. Munoz, R.K. Singh, N. Salazar, J.J. Hoy, B.L. Lokeshwar, beta-Arrestin-2 counters CXCR7-mediated EGFR transactivation and proliferation, Mol. Cancer Res. 14 (2016) 493–503, https://doi.org/10.1158/1541-7786.MCR-15-0498.