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MODESTUM

Case Report **OPEN ACCESS**

Osimertinib induced cardiac failure and atrial flutter in a patient with advanced pulmonary adenocarcinoma: A case report and review of the literature

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ABSTRACT

Background: Osimertinib-induced cardiotoxicity is a significant but rare condition. This article reports a case of an elderly patient who developed cardiac failure and atrial flutter due to Osimertinib treatment, potentially related to both the drug and the patient's underlying factors.

Case presentation: A 63-year-old man diagnosed with advanced non-small cell lung cancer (NSCLC) with bone metastasis was found to have an epidermal growth factor receptor mutation (exon 19 deletion). He had undergone four prior treatment regimens, including afatinib and bevacizumab. After two years, he developed resistance and experienced brain and bone metastases, prompting a switch to Osimertinib (80 mg/day). Before starting Osimertinib, he had a history of coronary artery disease and hypertension, with a normal electrocardiogram (ECG) and a left ventricular ejection fraction (LVEF) of 53%. However, nearly two months after initiating Osimertinib, he was presented with cardiac failure symptoms, with LVEF decreasing to <53% and atrial flutter observed on ECG. Suspecting drug-induced cardiotoxicity, Osimertinib was discontinued. Following cessation of the drug, his cardiac function improved, and the ECG abnormalities resolved. This case represents the first reported instance of concurrent cardiac failure and atrial flutter associated with Osimertinib treatment.

Conclusions: As Osimertinib continues to significantly enhance survival in NSCLC, there remains a need for active monitoring of cardiac adverse events in patients undergoing Osimertinib treatment. These events can be life-threatening but are usually reversible after discontinuation of the drug.

Keywords: Osimertinib, cardiac failure, atrial flutter, epidermal growth factor receptor

INTRODUCTION

Osimertinib is a third-generation, tyrosine kinase inhibitor (TKI) of epidermal growth factor receptor (EGFR) that is selective for EGFR-TKI–sensitizing and T790M-resistant mutations in patients with advanced non-small cell lung cancer (NSCLC). Cardiotoxicity is a rare but important adverse event (AE) of treatment. A retrospective study of cardiac AEs from 2016 to 2018 indicated that, compared with other EGFR-TKIs, Osimertinib remarkably increased the risk of cardiotoxicity such as cardiac failure, QT prolongation, atrial fibrillation, pericardial effusion and pericardial effusion [1]. Meanwhile, a meta-analysis of key studies showed that Osimertinib was associated with cardiac failure and QT prolongation [2]. To our knowledge, heart failure and QT prolongation caused by Osimertinib have been reported, but no cases of atrial flutter have been reported so far. Herein, we report a rare and significant case of Osimertinib-generated cardiotoxicity in which heart failure and atrial flutter occurred simultaneously.

In the early clinical application of the first-generation EGFR-TKIs (such as gefitinib and erlotinib), various degrees of cardiovascular toxicity were noted. For instance, gefitinib is associated with acute coronary syndrome [3]. The second-generation EGFR-TKIs, including afatinib and dacomitinib, also exhibit cardiotoxic effects; afatinib has been reported to cause a decrease in left ventricular ejection fraction (LVEF) [4], while dacomitinib may lead to hypertension [5]. Although third-generation EGFR-TKIs, such as Osimertinib, demonstrate superior efficacy, their cardiotoxicity is notably higher compared to the first and second generations. A retrospective study based on the FDA AE reporting system indicated that Osimertinib significantly increases the risk of QT interval prolongation, heart failure, and atrial fibrillation compared to the first and second-generation EGFR-TKIs [1]. The issue of QT interval prolongation associated with Osimertinib was initially identified in a large phase III clinical trial (AURA3 study) [6], which compared the efficacy and safety of Osimertinib versus standard chemotherapy (pemetrexed plus platinum) in patients with advanced NSCLC harboring the EGFR T790M mutation. The results showed that over 4% of patients in the Osimertinib group experienced QT interval prolongation (most

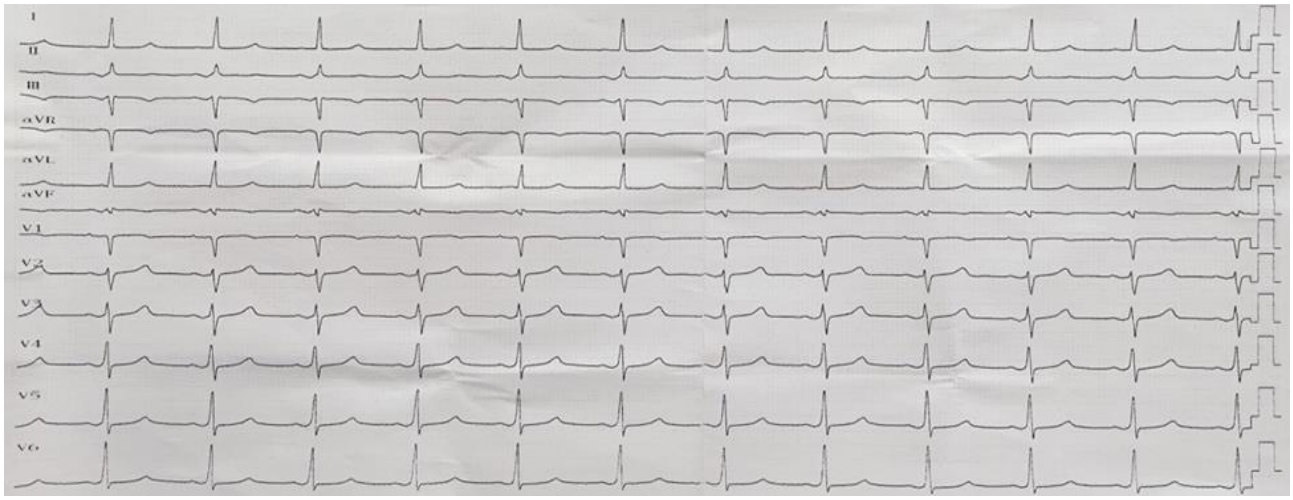

Figure 1. ECG before initiation of Osimertinib (Reprinted with permission of the patient)

of which were graded 1-2), and an additional 5% exhibited a decrease in LVEF. In another randomized controlled trial (FLAURA study) [7] comparing Osimertinib with the first-generation EGFR-TKIs, 10% of patients in the Osimertinib group experienced QT interval prolongation, compared to only 4% in the control group (gefitinib or erlotinib). Moreover, the incidence of decreased LVEF was 3% in the Osimertinib group versus 1% in the control group. These findings provide important background for understanding the differences in cardiotoxicity among EGFR-TKIs and may help optimize clinical treatment strategies.

CASE PRESENTATION

A 63-year-old man with a smoking history of 30 packs per year was diagnosed with advanced lung adenocarcinoma three years prior. He suffered from low back pain and was admitted to our hospital on 21 April 2021. In April 2017, the patient visited hospital due to cough, expectoration and abdominal discomfort. Chest CT revealed space-occupying lesions in the right upper lung, identified as lung cancer with obstructive pneumonia. Right pleural effusion, pericardial effusion, and right hilar and mediastinal lymph node enlargement were also observed on CT. Brain MRI showed no abnormal signs. PETCT: partial rib and lumbar vertebra had higher levels of glucose metabolism, suggestive of lung cancer bone metastasis. Multiple enlarged lymph nodes were found in bilateral neck, clavicular area, mediastinum, right hilum, small omental sac, mesenteric root and retroperitoneum, indicating multiple lymph node metastasis. Then lung adenocarcinoma was confirmed by a cervical lymph node biopsy. The stage after assessment was T4N3M1c, stage IVB. Genetic testing showed that an EGFR mutation of exon 19 deletion. The patient was given four regimens of treatment including conmana 125 mg tid + bevacizumab and cisplatin doublet chemotherapy. In March 2018, re-examination of chest CT showed progression of tumor lesions and pericardial effusion increased. The patient was advised to undergo genetic testing again, but he refused and continued to take conmana. In March 2021, brain MRI indicated multiple brain lesions consistent with metastatic tumors. He started Osimertinib treatment (80 mg/day). Just prior to initiation of Osimertinib, his electrocardiogram (ECG) was normal (**Figure 1**). Meanwhile, echocardiography was conducted and revealed a LVEF of 53%.

At admission, during the initial examination, the vital signs including T 36.5 °C, blood pressure 100/64 mmHg, heart rate 86 beats/min, and respiratory rate 14 breaths/min. Blood routine: white blood cells 3.90 × 109/L, neutrophils 2.77 × 109/L, hemoglobin 58 g/L, platelets 272 × 109 /L. N-terminal pro-brain natriuretic peptide (NT-proBNP) 551 pg/mL. Serum creatinine 188 umol/L. Electrolytes: potassium 4.76 mmol/L. CEA3.79 ng/ml. Brain MRI: multiple abnormal signals were detected in both cerebellar hemispheres, vermis and bilateral cerebral hemispheres. Combined with medical history, metastasis was considered. Thoracolumbar MRI showed high signal in L1 and L2 vertebrae with surrounding soft tissue signals, also considering the possibility of metastasis. On the 16th day after admission, the patient was given pemetrexed treatment. Meanwhile, lumbar radiotherapy was also administered but was later suspended due to grade IV myelosuppression.

He had a history of coronary heart disease and stable hypertension. But he had no symptoms after long-term regular drug control. On 22 May 2021, nearly two months before the initiation of Osimertinib, he initially presented with dyspnea, tachycardia, palpitations, and bilateral lower limb edema. The screening echocardiography revealed a reduction of LVEF from 53% to 30% and his ECG was atrial flutter (**Figure 2**). Nearly 2 months prior to Osimertinib treatment his NT-proBNP was 551 pg/mL, while at that time his NT-proBNP was 35,594 pg/mL. To alleviate the symptoms, furosemide intravenously was preferred and then switched to oral furosemide and spironolactone. Magnesium supplementation, potassium supplementation, the antiarrhythmic drug amiodarone and the cardiotonic drug west orchid were also applied as part of the treatment. The unexpected cardiac failure and atrial flutter triggered by Osimertinib was strongly suspected and discontinued. The patient's symptoms improved after treatment, and he was discharged on 22 June 2021. Two months after Osimertinib discontinuation, his NT-proBNP decreased to 9,634 pg/mL, and LVEF improved to 36%; atrial flutter disappeared on ECG (**Figure 3**).

DISCUSSION AND CONCLUSIONS

EGFR-TKI has been applied in NSCLC patients with EGFR mutation. Osimertinib, the third-generation EGFR-TKI that was initially used in patients with T790M-positive NSCLC [6].

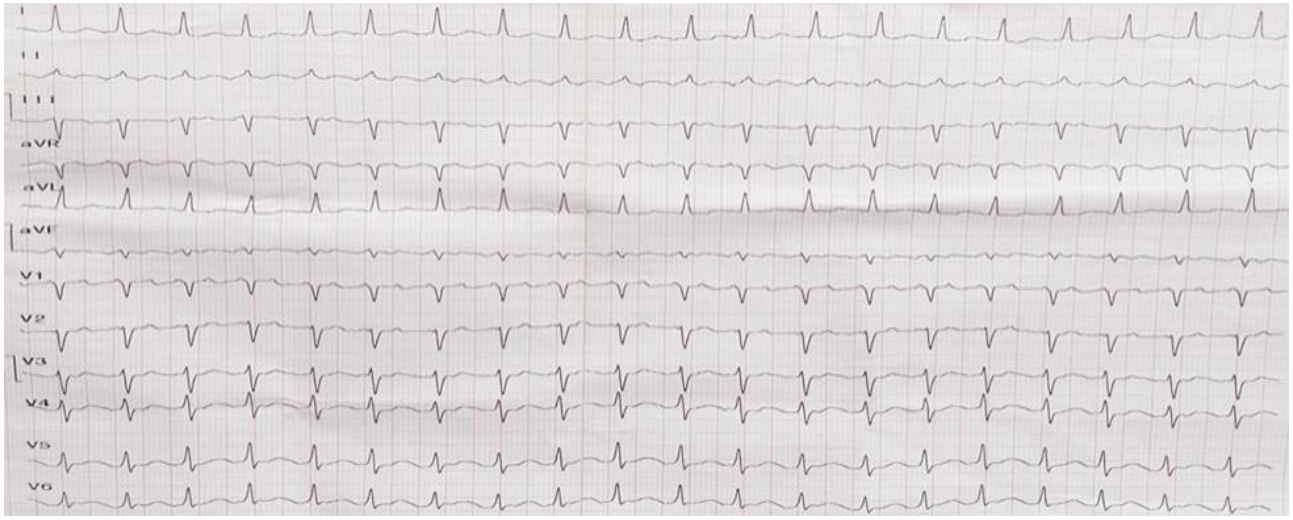

Figure 2. ECG showed atrial flutter after nearly 2 months of Osimertinib treatment (Reprinted with permission of the patient)

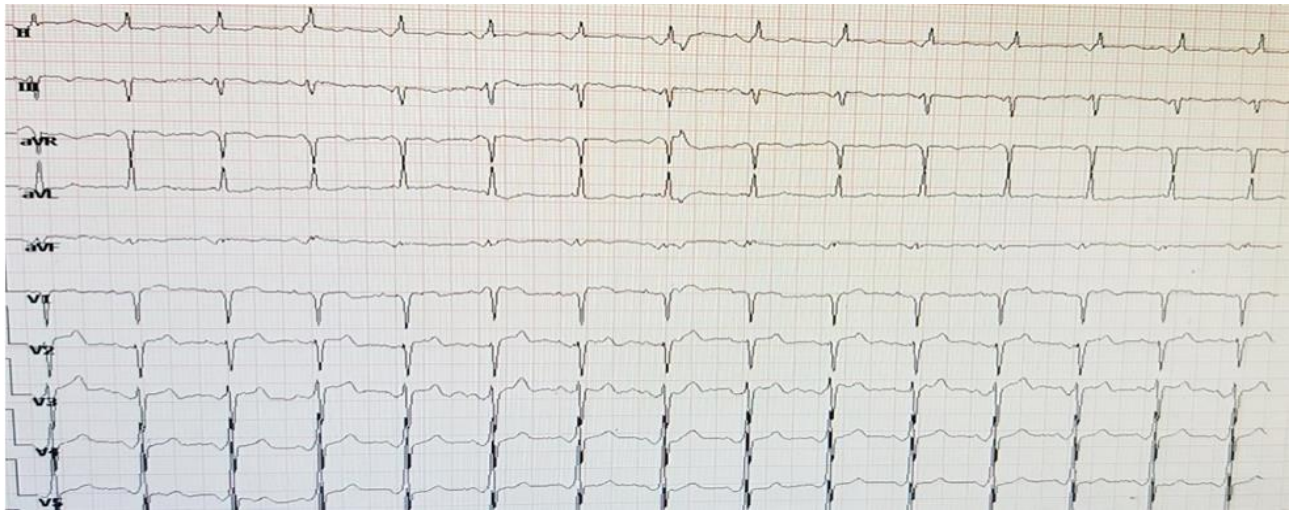

Figure 3. ECG showed atrial flutter disappeared after 2 months of Osimertinib discontinuation (Reprinted with permission of the patient)

Recently, Osimertinib has shown improved results in comparison with standard EGFR-TKIs in the frontline setting in patients with EGFR mutations, urging Osimertinib to be the preferred TKI for EGFR-mutated NSCLC [7]. Osimertinib has a good effect on brain metastasis.

Our patient was presented with brain and bone metastases, due to advanced NSCLC; thus, Osimertinib was given after progression of conmana treatment. EGFR-TKIs can be produced in a variety of adverse reactions such as rash, oral ulcers, diarrhea, interstitial lung disease, liver function damage, renal insufficiency, ocular toxicity and cardiotoxicity [8]. Cardiotoxicity is an infrequent but important AE of treatment. Osimertinib is associated with an increased risk of cardiotoxicity compared with the other EGFR-TKIs. A retrospective study about cardiac AEs on account of EGFR-TKIs in FAERS indicated that 315 AEs were noted, with 150 (6.1%) attributed to Osimertinib, 157 (2.7%) attributed to other TKIs, and 8 (5%) attributed to Osimertinib combined with other TKIs [1]. This study reported that the AEs including cardiac failure, atrial fibrillation, QT prolongation, myocardial infarction, and pericardial effusion. In addition, Osimertinib-induced myocarditis have been described [9]. The etiology of Osimertinib-induced cardiotoxicity is unknow. However, it is reported that it may be associated with HER2. Osimertinib inhibits not only EGFR but also HER2. HER2 is expressed in cardiomyocyte membranes and have an important effect on myocyte survival, growth, and stress responses [10].

A retrospective clinical study on cardiac AEs associated with Osimertinib showed that cardiac failure was the most common AE to ositinib [1]. A Japanese retrospective study also reported that severe cardiac AEs occurred in six patients, three of whom developed heart failure with reduced LVEF [11]. A decrease in LVEF was observed in just over a month, with the absolute value dropping to 30% in the echocardiography of our patient. Ositinib was contacted with a risk of untoward effects on left ventricular dysfunction, which begins with asymptomatic electrocardiographic changes, followed by left ventricular functional decrease, serious cardiac failure, and fluid retention progressively [12]. In order to facilitate early detection of drug-related AEs, evaluation of cardiac function was necessary. Thus, we recommend that clinicians perform echocardiography before and during EGFR-TKI therapy. The atrial flutter is influenced by various factors including age, gender, electrolytes, drugs, cardiac diseases, metabolic diseases, tumors and infection. Atrial flutter can worsen heart disease and lead to heart failure. Although AEs of atrial flutter

Table 1. Review of case reports of concomitant cardiotoxicity due to Osimertinib

R	A	S	EGFRM	SM	Cardiovascular disease history	Prior treatment	Cardiac event	Time to AE	Osimertinib effect	Osimertinib treatment	Cardiac outcome
[8]	85	M	L861Q + T7 90M	ND	ND	Geftinib	QT prolongation & torsade de pointes	0.5 months	ND	ND	QTC interval 496 Ms after 91h; torsade de pointes correction
[11]	78	F	L858R	N	Hypertension & thoracic aortic aneurysm	ND	Heart failure & QT prolongation	Months	PR	D	LVEF improved to 48% after 9 months
[11]	71	F	L858R + T790M	N	Hypertension	ND	Mitral regurgitation & mitral valve prolapse	Months	PR	D	Mitral regurgitation persisted
[11]	68	M	Ex.19 del + T790M	N	None	Gefifitinib + Erlotinib	QT prolongation, tricuspid valve regurgitation, & pulmonary hypertension	1 month	PR	Reduced dosage from 80 mg to 40 mg every other day	Tricuspid valve regurgitation persisted
[11]	64	F	L858R + T790M	Y	Moderate mitral regurgitation	Grlotinib	EF decline	9 months	PR	Restarted at 80 mg daily after LVEF improvement	LVEF retun to 62% after 14 months
[11]	52	F	L858R	Y	Obesity	ND	EF decline	Weeks	PR	D	LVEF recovered to 63% after 2 months
[11]	71	F	L858R	N	Hypertension & diabetes mellitus	ND	Acute myocardial infarction	2 months	NE	D	Improvement
[14]	84	F	L858R + Ex.19 del	Y	None	Stereotactic thoracic radiotherapy	Cardiac failure, QT prolongation, & torsade de pointes	Months	PD	D	LVEF improved to 51% after 4 months; QTC returned to normal; torsade de pointes correction
[15]	78	F	L858R + T790M	ND	ND	Erlotinib + bevacizum ab + platinum doublet chemotherapy	Cardiac failure	3 weeks	ND	D	Improvement
OC	63	M	Ex.19 del	Y	Hypertension & coronary heart disease	Conmana + bevacizum ab + platinum doublet chemotherapy	Cardiac failure & atrial flutter	Nearly 2 months	PD	D	LVEF improved to 36% after 2 months; atrial flutter disappeared

Note. R: Reference; OC: Our case; A: Age; S: Sex; M: Male; F: Female; EGFRM: Epidermal growth factor receptor mutation; SM: Smoking; ND: Not documented; Y: Yes; N: No; D: Discontinued; PR: Partial response; PD: Progressive disease; & NE: Not evaluable

caused by Osimertinib are rare, regular ECGs are recommended in patients taking Osimertinib. Dose reduction or treatment interruption should be performed for serious cardiotoxicity and serious arrhythmia [13]. Thus, we discontinued Osimertinib when the patient developed atrial flutter and decreased cardiac function.

This is a rare and simultaneously significant case in which cardiac failure and atrial flutter are induced by Osimertinib. As far as we know, several cases of concurrent cardiac dysfunction, QT prolongation, and torsade de pointes caused by Osimertinib have been reported (**Table 1**). However, no atrial flutter has been discovered so far. Unlike those cases, our patient had coronary heart disease. A retrospective analysis of cardiac AEs suggest that cardiac AEs may occur more commonly in patients with pre-existing cardiovascular disease [11]. Osimertinib may further worsen underlying cardiac pathology. However, the patient had previously received bevacizumab and cisplatin chemotherapy. According to reported the most common cardiovascular complication of bevacizumab therapy is arterial hypertension, other one is cardiac dysfunction [14]. A meta-analysis about breast cancer indicated that the frequency of cardiac dysfunction induced by bevacizumab was 1.6% [15]. Cisplatin also carries a risk of heart dysfunction. Cisplatin-containing chemotherapy may produce significantly higher risk of ischemic heart disease or heart failure in patients over 65 years of age [16]. Chemotherapy can damage both cardiomyocytes and vasculature. This chemotherapy-induced secondary reaction concerning heart disease is often ignored, because it can be asymptomatic. Consequently, recognizing the risks for cardiac dysfunction is of crucial importance in clinical practice.

For patients with pre-existing cardiovascular conditions who are treated with Osimertinib, it is essential to implement a comprehensive long-term management plan. This should include regular cardiac monitoring through baseline and periodic assessments, such as echocardiograms and ECGs, to evaluate cardiac function, particularly LVEF and QT intervals. Consideration of cardioprotective agents, like beta-blockers or angiotensin-converting enzyme inhibitors, may be warranted based on the individual patient's cardiovascular risk factors. Additionally, personalized treatment adjustments should be made for patients showing signs of cardiotoxicity, which may involve dose modifications or switching to alternative therapies if necessary. A multidisciplinary approach, involving cardiologists, oncologists, and primary care physicians, can further enhance patient management by ensuring all aspects of the patient's health are monitored and addressed. By adopting these strategies, the risk of severe cardiac events in patients receiving osimertinib can be minimized while still providing effective cancer treatment.

In conclusion, as Osimertinib continue to significantly enhance survival in NSCLC, there still remains a need to actively monitor patients for cardiac AEs during treatment with

Osimertinib. As it can lead to life-threatening but is usually reversible after discontinuation.

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Ethical statement: The authors stated that the study followed ethical procedures and received approval from the Ethics Committee of The Second Hospital of Nanjing affiliated with Nanjing University of Chinese Medicine, with approval number 2022-LY-ky042, granted on March 4, 2022. Before the study commenced, participants were provided with detailed information about the procedures and signed informed consent documents, ensuring that they fully understood the purpose of the research and the associated risks prior to their participation. The authors further stated that all sensitive and confidential personal data were kept strictly confidential, and the research team implemented necessary measures to protect participants' privacy, ensuring that the data were used solely for the purposes of this study and in compliance with relevant laws and regulations.

Declaration of interest: No conflict of interest is declared by the authors.

Data sharing statement: Data supporting the findings and conclusions are available upon request from the corresponding author.

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