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QT interval prolongation related to afatinib treatment in a patient with metastatic non–small-cell lung cancer

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ABSTRACT

Afatinib improves survival in metastatic non–small-cell lung cancer driven by activating epidermal growth factor receptor mutations. QT interval prolongation is a possible side effect of targeted anticancer drugs, but this has not been reported before with afatinib. We report a case of metastatic pulmonary adenocarcinoma with epidermal growth factor receptor exon 19 deletion who was treated with first-line afatinib. The patient was started on afatinib with a total dose of 40 mg/day and experienced grade 3 (>500 ms) QT interval prolongation in the seventh week. Dose was interrupted and then reduced to 30 mg/day after the event repeated. QT prolongation occurred only once with the reduced dose and radiologic oligoprogression was detected. Local therapy was performed and afatinib was continued as 30 mg/day. To the best of our knowledge, this case marks the first QT interval prolongation associated with afatinib. It is prudent to perform a baseline cardiologic evaluation and electrocardiogram monitoring in non-small cell lung cancer patients treated with this drug.

☆ The authors have no conflicts of interest to disclose.

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Introduction

Long-term outcomes of advanced non–small-cell lung cancer (NSCLC) patients harboring activating epidermal growth factor receptor (EGFR) mutations have significantly improved with emerging of anti-EGFR tyrosine kinase inhibitors (TKIs). One of these agents, afatinib is a selective and irreversible TKI which targets transmembrane receptors ErbB1 (EGFR), ErbB2 (HER2) and ErbB4.[1] Randomized phase III trials of EGFR mutant metastatic NSCLC comparing afatinib with cisplatin-based chemotherapy in first-line setting demonstrated that progression-free survival in all patients and overall survival in patients with EGFR exon 19 deletion were superior in afatinib arm.[2-4] In the United States, afatinib was approved in 2013 for first-line treatment of metastatic NSCLC harboring EGFR exon 19 deletion or exon 21 L858R mutation.

Cardiotoxicity is a major concern during ErbB-targeted and TKI therapy. There has only been one report of afatinib-related cardiac toxicity so far, which showed a decrease in left ventricular ejection fraction (LVEF).[5] Here we present a case of QT prolongation related to afatinib therapy developed in a metastatic NSCLC patient who had no underlying cardiac disease.

Case report

A 42-year-old female applied to the pulmonary medicine department of our institute with newly onset exertional dyspnea. She previously presented to a cardiology department in another institute where pericardial effusion was detected, subsequently she was started on colchicine and ibuprofen. Her thoracic computed tomography scans revealed a 2 cm mass in her left lung and mediastinal lymphadenopathies. Her medical history was unremarkable except 30 pack-years of formerly smoking. Baseline ^{18}F-FDG PET/CT showed a 2 cm malignant nodule in upper lobe of left lung along with metastases in multiple mediastinal and supraclavicular lymph nodes, intra-abdominal lymph nodes, left adrenal gland and bones (Fig. 1A). Core biopsy of the pulmonary nodule did result as primary lung adenocarcinoma. Shortly thereafter patient presented with progressive dyspnea and sudden-onset chest pain to our emergency department and she was diagnosed with pericardial tamponade. Pericardiocentesis was performed and cytology revealed dissemination of pulmonary adenocarcinoma. Maximum thickness of pericardial effusion decreased from 41 to 5 mm within 1 week of admission and no more fluid accumulated again therefore her pericardial catheter was removed. There was also no pericardial mass on echocardiography and corrected QT interval (QTc) on electrocardiogram (ECG) was calculated as 439 ms. Contrast cranial magnetic resonance imaging showed multiple metastases which were irradiated with whole brain radiotherapy.

The patient was then referred to the medical oncology division of our institute. Real-time polymerase chain reaction of her lung biopsy specimen revealed EGFR exon 19 deletion and she was subsequently started on afatinib 40 mg/day. After 3 weeks of treatment, ECG was unremarkable except T-wave inversion in leads I and aVL, which was evaluated by cardiology department and echocardiogram showed only pericardial effusion with a maximum thickness in the posterior heart wall measured as 7 mm. Afatinib was continued as 40 mg/day. Follow-up ECG after 4 weeks manifested a QTc interval of 504 ms, which corresponded to grade 3 toxicity according to Common Terminology Criteria for Adverse Events Version 5.0, although she did not describe any cardiac symptoms (Fig. 2A). At this time serum sodium was measured as 131 mEq/L, potassium as 5.1 mEq/L and corrected calcium as 9.4 mg/dL. Meanwhile her other medications were also re-

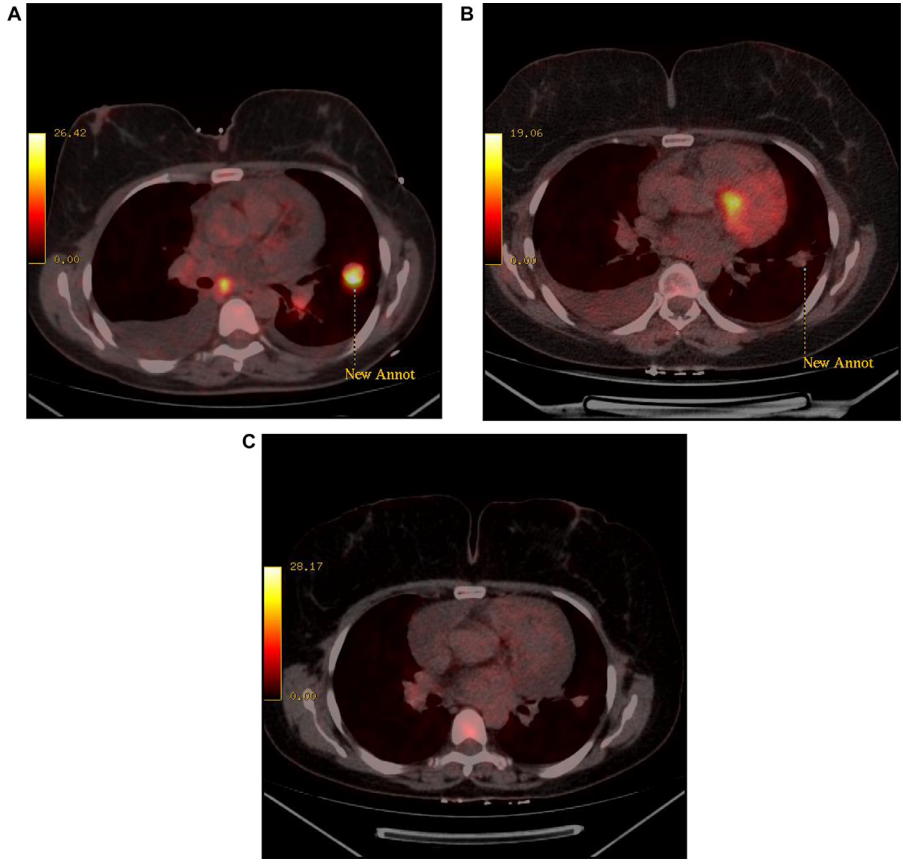

Fig. 1. ^{18}F-FDG PET/CT scans of the patient. (A) Baseline scan showing primary nodule in upper lobe of left lung (dashed line). (B) Partial response in primary nodule at 10th week of treatment (dashed line). (C) Stable primary nodule and new metastatic lesion in T6 vertebrae at 32nd week of treatment.

viewed and recorded as pregabaline 150 mg/day, colchicine 1 mg/day, tramadol 200 mg/day and mirtazapine 30 mg/day. However, afatinib was thought to be responsible for QTc prolongation, therefore treatment was interrupted for one week, at the end of which QTc decreased to 447 ms and afatinib was restarted as 40 mg/day (Fig. 2B). ^{18}F-FDG PET/CT after 10 weeks of treatment showed partial responses in primary lesion, mediastinal lympohadenopathies and left acetabular lytic/sclerotic lesion; and also no pathological FDG uptake was reported in left adrenal gland, intraabdominal lymphadenopathies and remaining bone metastases (Fig. 1B). Two weeks later, QTc was measured as 537 ms, but the patient was asymptomatic again (Fig. 2C). Serum sodium was 137 mEq/L, potassium 4.3 mEq/L, corrected calcium 8.8 mg/dL and magnesium 2.3 mg/dL. Afatinib dose was subsequently reduced to 30 mg/day. After 6 weeks of follow-up QTc was 481 ms and afatinib was continued as 30 mg/day. Four weeks later, an asymptomatically prolonged QTc of 511 ms was detected. Her serum electrolytes were all in normal range again: sodium 143 mEq/L, potassium 4 mEq/L, corrected calcium 9.9 mg/dL and magnesium 1.9 mg/dL. The patient was still on pregabaline, colchicine and mirtazapine; all doses were the same as mentioned above. A 24-hour holter ECG was performed as suggested by the cardiology department and it showed sinus rhythm with a mean heart rate of 71/min. One week later, QTc was measured as 436 ms and the cardiology department approved the continuation of afatinib since there was not a significant arrhythmia on holter ECG. Afatinib was continued with a dose of 30 mg/day

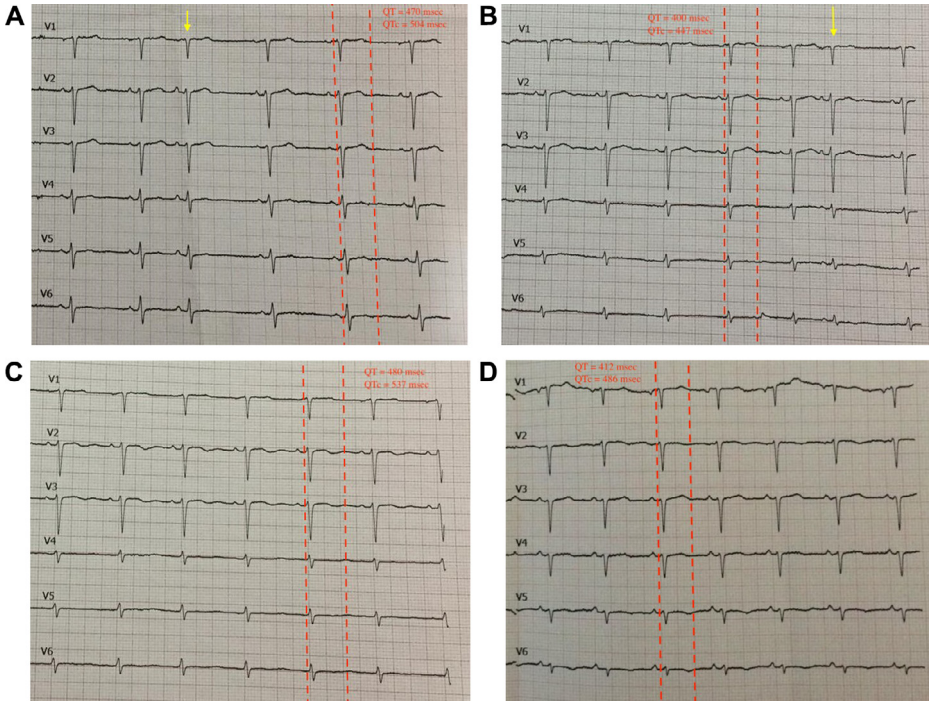

Fig. 2. Electrocardiograms (ECGs) of the patient. Red dotted lines indicate QT intervals and QT and QTc measurements. Yellow arrows indicate atrial ectopic beats. QTc interval was 504 ms at 7th week of treatment (A), and after interrupting afatinib dose for 1 week, it decreased to 447 ms (B). Afatinib dose was reduced to 30 mg/day after second QTc prolongation (C). Last ECG on 30 mg/day dose showed QTc interval of 486 ms (D).

and QTc interval did not prolong during follow-up. After a 20-week course of 30 mg/day afatinib (interrupted only for 1 week) ^{18}F-FDG PET/CT was performed to assess treatment response. Primary lesion in the left lung was reported as stable and there was no progression in other findings, only lesions in T6 and L3 vertebrae had a mild increase in FDG uptake (Fig. 1C). Palliative radiotherapy was administered to these lesions because she also suffered from back pain. Afatinib was continued 30 mg/day dose, on which the patient had no further cardiac adverse events and she is still on the same dose with stable disease (Fig. 2D).

Discussion

Afatinib is an established front-line option in metastatic NSCLC harboring activating EGFR mutations but also has a potential of cardiac toxicity due to its mechanism of action. We report a case of metastatic NSCLC in whom QT prolongation occurred under afatinib therapy, which was then successfully managed with dose interruption and reduction. To the best of our knowledge, this is the first case of QT prolongation associated with afatinib and the second report of cardiac adverse event related to the drug.

Cancer patients are susceptible to QT prolongation, for which risk factors are genetic predisposition, electrolyte disorders (hypokalemia, hypocalcemia, and hypomagnesemia), treatment-related toxicities (emesis, diarrhea), hypothyroidism and concomitant drugs (antidepressants, antiemetics, antibiotics, antihistamines, etc.).[6] Cardiovascular toxicity including QT prolongation can also occur with TKI treatment. Mechanisms of TKI-related QT prolongation are still not well-understood; possible explanations include an interaction with human kinases responsible for

cardiac functions through competition for adenosine triphosphate binding pockets and ion (especially potassium) channel blockade.[7,8]

Data from clinical trials concerning afatinib showed no significant effect of the drug on cardiac functions. A phase II trial, which enrolled 60 patients with relapsed or refractory solid tumors treated with afatinib 50 mg/day, did not show any prolongation of QTc interval or any effect on heart rate.[9] There was no significant change in LVEF with afatinib in the phase IIb/III LUX-Lung 1 trial, which compared 50 mg/day afatinib with placebo in patients with advanced NSCLC who progressed after 1 or 2 lines of chemotherapy and one anti-EGFR therapy as erlotinib or gefitinib.[10] Regarding the first-line randomized phase III trials of the drug, safety analysis of LUX-Lung 3 did not show any treatment-related cardiac event with afatinib and there were no afatinib-related ECG changes reported in LUX-Lung 6.[2,3] Data collected from LUX-Lung 1 and LUX-Lung 3, which also included a pooled analysis of 49 trials, indicated that there was no clinically significant reduction in LVEF with afatinib, but could not exclude rare cardiovascular events in patients with limited reserves.[11] A systematic review of cardiovascular safety data from clinical trials on anticancer therapies assigned afatinib to have a very low risk of QTc prolongation, stating an incidence of less than 1%.[12] In contrast to low probability of inducing QTc prolongation as suggested by the safety data from clinical trials, our case demonstrates that this adverse event may occur with afatinib even when there is no underlying cardiac disease and affect treatment process considering its severity as reported in the presentation.

Our case had not any long-standing cardiac disease but presented with pericardial tamponade due to the underlying malignancy. We did not consider this to be confounding because pericardial effusion had already resolved and QTc interval was not prolonged prior to start of afatinib. Serum electrolytes were all in normal range at the time of first QTc prolongation under afatinib and the patient was still on colchicine, tramadol and mirtazapine. While these drugs also may carry a possible risk of prolonged QTc interval, typical resolution of the event following interrupting and decreasing afatinib dose strongly supports an association with afatinib itself. Oligoprogression in subsequent PET/CT findings under 30 mg/day of afatinib gives rise to the thought that efficacy of the drug can be maintained even with a reduced dose.

In conclusion, afatinib may cause QTc prolongation even though data from preclinical and clinical trials demonstrate no such significant adverse effect. Therefore, baseline cardiac evaluation and close follow-up with ECG should take place in the treatment of advanced NSCLC with this agent.

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