OMCR

Oxford Medical Case Reports, 2019;01, 47–51

doi: 10.1093/omcr/omy122
Case Report

CASE REPORT

Amiodarone-induced life-threatening torsade de pointes in an end-stage lung cancer patient receiving gefitinib

Dan Han[1], Hui Tan[2], Chaofeng Sun[1] and Guoliang Li[1,*]

[1]Department of Cardiovascular Medicine, First Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China, and [2]Department of Respiratory Medicine, First Affiliated Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China

*Correspondence address. First Hospital of Xi'an Jiaotong University, 277 Yanta West Road, Xi'an 710061, China. Tel/Fax: +86-29-85-32-35-24; E-mail: liguoliang_med@163.com

Abstract

The risk factors of acquired long QT syndrome (aLQTS) are sometimes overlooked in clinics. Drugs, hypokalemia, age and female sex are well-known risk factors of QT prolongation-dependent torsade de pointes (TdP), which explains the high incidence of sudden cardiac death in LQT patients. Here, we report a case of an elderly female patient with lung cancer who was in poor condition, for whom amiodarone was mistakenly prescribed to rectify premature ventricular contractions. QT prolongation-dependent TdP immediately followed intravenous injection of amiodarone. Fortunately, the patient survived aborted sudden cardiac arrest after effective cardio-pulmonary resuscitation and electric defibrillation. Upon reviewing the clinical information, several pre-existing risk factors of aLQTS and TdP were identified. The mistaken prescription of amiodarone provoked TdP after these risk factors were overlooked in this case and thus predisposed this patient to a high susceptibility of drug-induced TdP.

INTRODUCTION

Drug-induced long QT syndrome (LQTS) is the most common type of acquired long QT syndrome (aLQTS). It has been proposed that a fraction of individuals with borderline, or even normal QT-intervals, but in possession of risk factors of QT prolongation, are predisposed to life-threatening arrhythmias due to drug exposure [1]. End-stage diseases or poor conditions such as multiple organ failure, dyscrasia, hypoxia, and disturbance of acid-base and electrolyte balances, predispose patients to outbursts of malignant arrhythmias or even sudden cardiac death (SCD). Torsade de pointes (TdP) is a kind of polymorphic ventricular tachycardia (VT) that results from QTc prolongation, particularly more than 500 ms [2].

Amiodarone used to treat atrial and/or ventricular arrhythmias [3] and verified to reduce mortality in sufferers with structural heart malfunctions [4]. Administration of intravenous amiodarone has been reported to cause TdP in some patients who have a reduced repolarization reserve, which is a risk factor for TdP [5]. Here, we report a patient with advanced nonsmall cell lung cancer (NSCLC), chronic obstructive pulmonary disease (COPD), and chronic heart failure (CHF), who developed TdP following the mistaken administration of intravenous amiodarone for premature ventricular contractions (PVCs).

CASE REPORT

An 85-year-old woman was transferred to our emergency department due to respiratory failure. Electrocardiogram (ECG) in the

Received: July 16, 2018. **Revised:** October 25, 2018. **Accepted:** November 7, 2018

emergency department displayed a sinus rhythm of 100 bpm, QT interval of 400 ms and QTc of 516 ms (Fig. 1). Her initial diagnosis was advanced NSCLC, COPD and CHF with electrolyte disturbance. Physical examinations showed blood pressure of 142/102 mmHg and bilateral cardiac enlargement. Laboratory examinations revealed PaO_2 of 68 mmHg, $PaCO_2$ of 55 mmHg, base excess of 5.80 mmol/l, serum K^+ concentration of 3.30 mmol/l, Mg^{2+} concentration of 0.94 mmol/l, Ca^{2+} concentration of 0.76 mmol/l and NT-proBNP > 35,000.00 pg/ml. Echocardiography showed bilateral cardiac enlargement, severe valve regurgitation, pulmonary arterial hypertension and a left ventricular ejection fraction (LVEF) of 30%. On the first day after admission, ECG (Fig. 2) in the Department of Respiratory Medicine displayed a sinus rhythm of 83 bpm, QT interval of 600 ms, and QTc interval of 706 ms. Treatments, including antineoplastic gefitinib (250 mg/d, per os), antibiotics mezhocillin sodium (0.1 g/min, iv) and sulbactam sodium (25 mg/min, iv), continuous low flow oxygen (3 l/min), and electrolyte and acid-base balancing, as well as other conventional treatments, were given.

On the second day after admission, the patient experienced several PVCs (originally ECG not obtained). Mistakenly, intravenous injection of amiodarone (1 mg/min) was then given to rectify the arrhythmia. After approximately half an hour, ECG monitoring showed TdP (Fig. 3). Electrical cardioversion was utilized immediately. Ultimately, the patient survived from aborted SCD and regained sinus heart rate. After consultation of cardiologists, amiodarone was stopped. Simultaneously, urgent laboratory examinations revealed pH of 7.48, PaO_2 of 91 mmHg, $PaCO_2$ of 44 mmHg, base excess of 6.60 mmol/l, serum K^+ concentration of 3.23 mmol/l, Mg^{2+} concentration of 0.92 mmol/l and Ca^{2+} concentration of 1.52 mmol/l. In the days after stopping amiodarone, the patient still displayed multiple electrolyte disturbances of hypokalemia and hypocalcemia, and the follow-up ECGs showed prolonged QTc (Fig. 4).

DISCUSSION

The pathophysiological foundation of LQTS depends on reduced electrical stability in the ventricle with increased APD heterogeneity [2]. The increased inward currents prolong phase 2 repolarization, then promote the occurrence of early and delayed afterdepolarizations (EADs and DADs), thus increasing the transmural dispersion of ventricular repolarization and leading to spontaneous diastolic depolarization. This cascade reaction promotes the spatial and temporal dispersion of ventricular repolarization, ultimately causing arrhythmic events that manifest as TdP on an ECG [6].

TdP can be initiated by types of ventricular arrhythmias [7]. A so-called 'pause dependent' phenomenon is a typical mode of onset of TdP in patients with acquired or congenital LQTS [8, 9]. The sudden change in ventricular activation does not allow for the accurate adaptation of ventricular APD; it reduces the

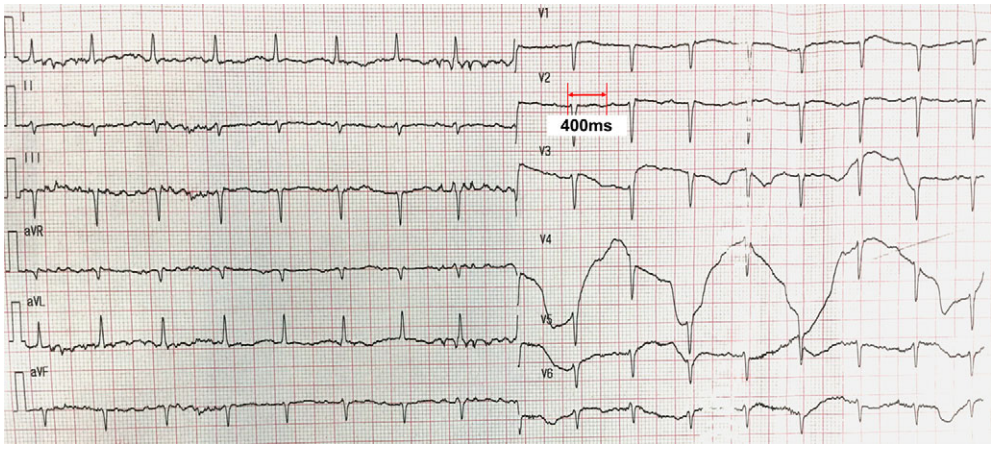

Figure 1: ECG tracing in the emergency room. Sinus rhythm of 100 bpm, QT of 400 ms, and QTc of 516 ms.

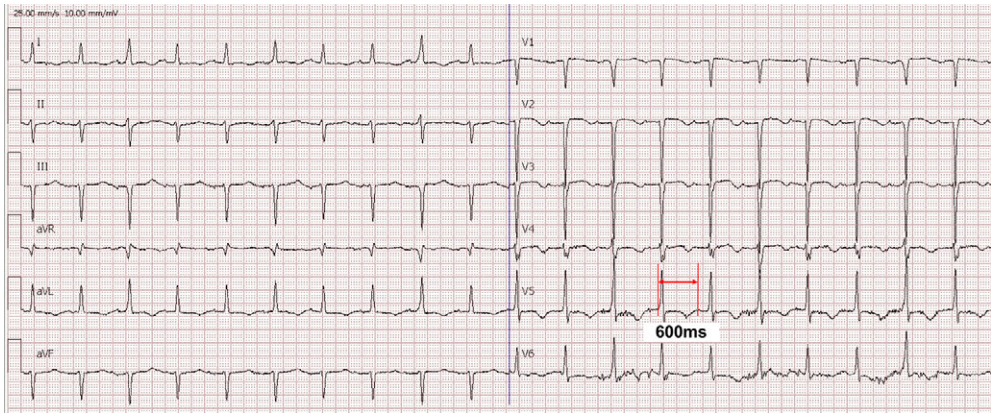

Figure 2: ECG tracing before TdP. Sinus rhythm of 83 bpm, QT of 600 ms, and QTc of 707 ms.

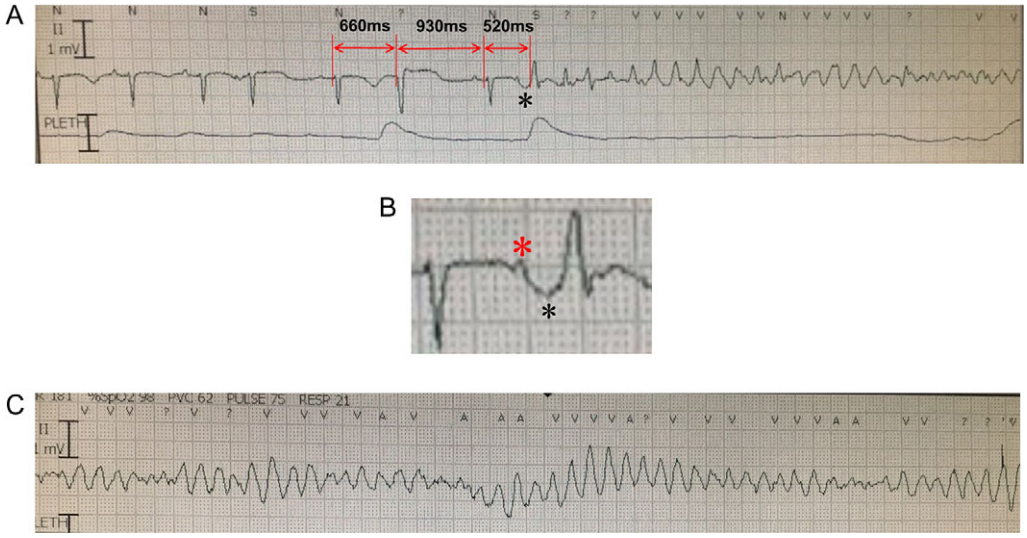

Figure 3: The monitoring electrocardiogram shows that TdP is induced by the short-long cardiac cycles and is followed by an initiating PVC (**A**). The initiating PVC appears after the T-wave peak of the last beat before the onset of TdP. The red asterisk indicates atrial premature complexes not conducted to the ventricle. However, if the atrial impulse propagates through the atrioventricular node and into the cardiac ventricles, it may induce TdP [17] (**B**). TdP strip (**C**).

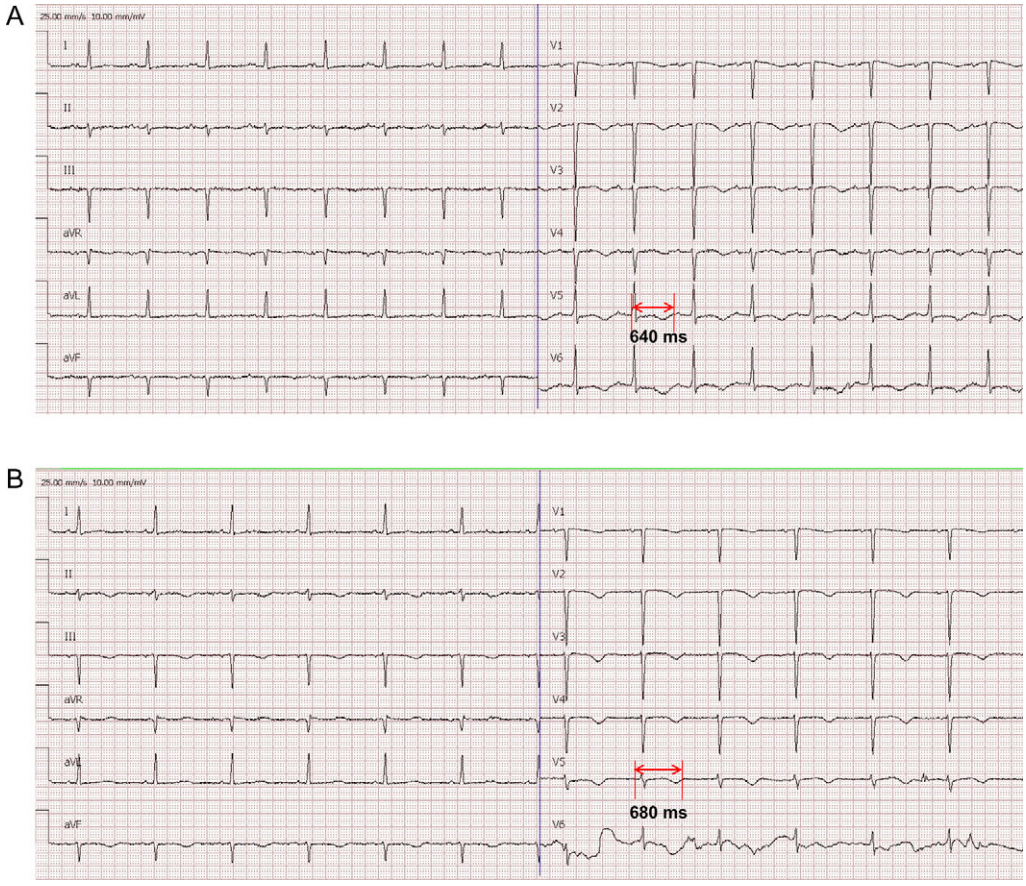

Figure 4: ECG tracings at 4 h (**A**) and 3 days (**B**) after successful effective cardio-pulmonary resuscitation and electric defibrillation. (**A**) Sinus rhythm of 68 bpm, QT of 640 ms and QTc of 682 ms. (**B**) Sinus rhythm of 54 bpm, QT of 680 ms and QTc of 643 ms.

repolarization reserve of the ventricle and thus possibly leads to TdP [7, 10].

Amiodarone has all four classes of electrophysiological features because it blocks various ion channels, such as I_{Kr}, I_{Ks}, I_{Na}, I_{CaL} and I_{to}, as well as adrenergic receptors and alpha receptor nuclear T3 receptor [11]. Amiodarone possesses antiarrhythmic effects in most cases, but also leads to a low prevalence of drug-induced TdP in some special cases [4, 12, 13].

Table 1: Every specific score of Naranjo algorithm of this patient

Questionnaire	Score
Are there previous conclusive reports on this reaction?	1
Did the adverse events appear after the suspected drug was given?	2
Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	1
Did the adverse reaction appear when the drug was readministered?	0
Are there alternative causes that could have caused the reaction?	−1
Did the reaction reappear when a placebo was given?	0
Was the drug detected in any body fluid in toxic concentrations?	0
Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	0
Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	0
Was the adverse event confirmed by any objective evidence?	1

In this case, there were multiple risk factors reducing repolarization reserve, but were overlooked. The patient was given mezlocillin sodium and sulbactam sodium as antibiotics; the adverse effects of these antibiotics with regard to cardiomyocytes and QTc prolongation have not been found in the literature. Other conventional treatments, particularly potassium and calcium supplements, were employed to maintain the balance of electrolytes. However, this patient received antineoplastic gefitinib with the potential of prolonging the QT interval [14, 15], and other risk factors facilitating drug-induced TdP included old age, female sex, hypokalemia, infection, COPD and CHF. All these factors predisposed this patient to the potential of QT prolongation-induced TdP. After amiodarone was mistakenly prescribed, TdP occurred. We calculated the score according to the Naranjo algorithm to evaluate the potential of amiodarone; the patient received a score of 4, suggesting possible adverse drug reaction due to amiodarone (Table 1) [16]. Therefore, amiodarone provoked TdP after being combined with risk factors that already existed.

Work has been done in this field with tools such as CiPA (Comprehensive in vitro Proarrhythmia Assay) to state the clinical risk of acquired arrhythmia; however, some clinicians are unaware of this important topic, unfortunately putting their patients to a high risk of drug-induced TdP, which can have fatal consequences.

CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest.

FUNDING

The authors report no targeted funding for this work.

ETHICAL APPROVAL

This case report was approved by the First Affiliated Hospital of Xi'an Jiaotong University ethics committee and was carried out in accordance with the principles of the Declaration of Helsinki. Both verbal and written informed consent were obtained from the patient before submission.

CONSENT

The case report contains no direct patient identifiers and no relevant indirect identifiers (as specified in the journal policy). The patient was explicitly and adequately informed by the corresponding author regarding the potential publication of this case.

GUARANTOR

The correspondence author guarantees for the accuracy of the data and the article.

REFERENCES

1. Roden DM. Drug-induced prolongation of the QT interval. *N Engl J Med* 2004;**350**:1013–22.
2. Saenen JB, Vrints CJ. Molecular aspects of the congenital and acquired Long QT Syndrome: clinical implications. *J Mol Cell Cardiol* 2008;**44**:633–46.
3. Connolly SJ. Evidence-based analysis of amiodarone efficacy and safety. *Circulation* 1999;**100**:2025–34.
4. Kodama I, Kamiya K, Toyama J. Cellular electropharmacology of amiodarone. *Cardiovasc Res* 1997;**35**:13–29.
5. Splawski I, Timothy KW, Tateyama M, Clancy CE, Malhotra A, Beggs AH, *et al*. Variant of SCN5A sodium channel implicated in risk of cardiac arrhythmia. *Science* 2002;**297**:1333–6.
6. Han D, Tan H, Sun C, Li G. Dysfunctional Nav1.5 channels due to SCN5A mutations. *Exp Biol Med* 2018;**243**:852–63.
7. Noda T, Shimizu W, Satomi K, Suyama K, Kurita T, Aihara N, *et al*. Classification and mechanism of Torsade de Pointes initiation in patients with congenital long QT syndrome. *Eur Heart J* 2004;**25**:2149–54.
8. Viskin S, Alla SR, Barron HV, Heller K, Saxon L, Kitzis I, *et al*. Mode of onset of torsade de pointes in congenital long QT syndrome. *J Am Coll Cardiol* 1996;**28**:1262–8.
9. Li G, Zhang L. The role of mexiletine in the management of long QT syndrome. *J Electrocardiol* 2018;**51**;1061–65.
10. Costard-Jackle A, Goetsch B, Antz M, Franz MR. Slow and long-lasting modulation of myocardial repolarization produced by ectopic activation in isolated rabbit hearts. Evidence for cardiac 'memory'. *Circulation* 1989;**80**:1412–20.
11. Lehtonen A, Fodstad H, Laitinen-Forsblom P, Toivonen L, Kontula K, Swan H. Further evidence of inherited long QT syndrome gene mutations in antiarrhythmic drug-associated torsades de pointes. *Heart Rhythm* 2007;**4**:603–7.
12. Beckermann TM, McLeod K, Murday V, Potet F, George AL Jr. Novel SCN5A mutation in amiodarone-responsive multifocal ventricular ectopy-associated cardiomyopathy. *Heart Rhythm* 2014;**11**:1446–53.
13. Wu L, Rajamani S, Shryock JC, Li H, Ruskin J, Antzelevitch C, *et al*. Augmentation of late sodium current unmasks the proarrhythmic effects of amiodarone. *Cardiovasc Res* 2008;**77**:481–8.
14. Porta-Sanchez A, Gilbert C, Spears D, Amir E, Chan J, Nanthakumar K, *et al*. Incidence, diagnosis, and management

of QT prolongation induced by cancer therapies: a systematic review. *J Am Heart Assoc* 2017;**6**:e007724.
15. Rajtik T, Goncalvesova E, Varga ZV, Leszek P, Kusmierczyk M, Hulman M, *et al*. Posttranslational modifications of calcium/calmodulin-dependent protein kinase IIdelta and its downstream signaling in human failing hearts. *Am J Transl Res* 2017;**9**:3573–85.
16. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, *et al*. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;**30**:239–45.
17. Kawano H, Matsumoto Y, Arakawa S, Satoh O, Hayano M. Premature atrial contraction induces torsades de pointes in a patient of Takotsubo cardiomyopathy with QT prolongation. *Intern Med* 2010;**49**:1767–73.