

Torsades de pointes with pseudo-T wave alternans during rociletinib therapy: A novel manifestation of a rare side effect



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Introduction

As the field of cardio-oncology evolves, it has become apparent that many of the novel therapies are associated with QT-interval prolongation. The combination of the physical properties of the drugs themselves, in addition to the clinical symptoms of nausea, vomiting, and diarrhea that cause electrolyte abnormalities, and the medications to treat those symptoms, may all contribute to prolongation of the QT interval.¹

Small molecule tyrosine kinase inhibitors (TKIs) form a class of novel cancer agents that has been shown to be associated with QT prolongation. Newer-generation TKIs have demonstrated significant promise for the treatment of non-small cell lung cancer. However, treatment with rociletinib was associated with hyperglycemia in 22% of patients and corrected QT interval (QTc) prolongation of any grade in 12% of patients. Although all patients in the pivotal clinical trial with QT prolongation and hyperglycemia were successfully managed with dose reduction, the risk for ventricular arrhythmias remains an important clinical concern.²

The present case report illustrates how the interplay between effects of rociletinib, electrolyte imbalance, and treatment of concomitant hyperglycemia can contribute to QT prolongation and malignant ventricular arrhythmias. While the risk for QT interval prolongation is well known with this novel drug, no prior cases of torsades de pointes (TdP) had been reported at the time of this case report. Our

aim is to highlight the importance of awareness of proarrhythmia, close QT interval monitoring, and the complex interaction between electrolyte imbalance and glycemic control.

Case report

An 84-year-old man with stage IV epidermal growth factor receptor mutation-positive adenocarcinoma of the lung presented to the emergency room with severe hyperglycemia. Eight days prior to presentation, he was initiated on rociletinib, a third-generation TKI, at a dose of 625 mg orally twice daily as part of a clinical trial. During trial screening, an electrocardiogram (ECG) was remarkable only for first-degree atrioventricular block and a QTc by the Bazett formula of 450 ms. The patient had no prior history of cardiac disease or arrhythmias.

On day 3 of therapy, he was initiated on metformin when he developed hyperglycemia with a blood glucose over 300 mg/dL, a known side effect of rociletinib. However, he developed nausea and vomiting and was transitioned to glyburide by an outside endocrinologist. On the day of presentation, the patient had been seen by his oncologist and was found to have a blood glucose level of 501 mg/dL with increasing weakness. He was given 1.5 L of fluids in clinic and then was sent to the emergency department after discussion with his endocrinologist. The patient had taken his last dose of rociletinib the evening prior to admission.

Upon arrival to the emergency department, serum glucose was 460 mg/dL and potassium (K) was 4.4 mmol/L. A 12-lead ECG showed a QTc interval of 582 ms with pronounced T-wave abnormalities with beat-to-beat variation in amplitude, vector, and duration (Figure 1). The observed macroscopic T-wave changes were most pronounced after premature atrial contraction (PAC)-induced pauses.

Subsequent ECGs demonstrated inversion of T waves and further pseudo-T wave “alternans” pattern. Three hours after

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KEY TEACHING POINTS

- Novel immunological agents such as tyrosine kinase inhibitors carry a small but potentially fatal proarrhythmic risk for QT-interval prolongation and torsades de pointes.
- Awareness of this rare complication and the complex interaction between electrolyte and glycemic imbalance may be important as the field of cardio-oncology continues to grow.
- Macroscopic T wave alternans signifies significant vulnerability during repolarization and may be a harbinger of impending electrical instability.

initiation of an insulin drip, glucose fell modestly to 433 mg/dL (normal CO₂ 20 mmol/L), K was 4.0 mmol/L, magnesium (Mg) was 1.5 mEq/L, and the patient developed increasing burden of episodes of TdP, with QTc intervals measuring 675 ms with accentuated macroscopic T-wave changes (Figure 2). The patient ultimately went into pulseless TdP, which required external electrical defibrillation. A temporary pacemaker wire was placed with rapid institution of right ventricular pacing at 90 beats per minute, as increasing the heart rate decreases the QTc interval. This suppressed further runs of TdP. His electrolytes were checked with aggressive repletion to goal levels of K > 4.5 mmol/L and Mg > 2.5 mEq/L.

A transthoracic echocardiogram performed after the external defibrillation revealed normal left ventricular function and mild left atrial enlargement without valvular or

structural abnormalities. Coronary angiography was then performed to rule out ischemia as the etiology of the T-wave changes, which revealed no significant obstructive coronary artery disease. Serial troponin-I biomarkers were negative throughout his admission.

Over hospital days 3 to 5, the patient was weaned off of temporary pacing. The degree of QT interval prolongation improved daily, with a QTc of 564 ms on hospital day 3 and 469 ms by hospital day 5, at which point the patient was discharged home (Figure 3). At follow-up 2 days post-discharge, the patient's QT interval prolongation and the T-wave changes had completely resolved. On 30-day event monitoring with a loop recorder, the patient had no further arrhythmias.

Discussion

This case report highlights the potential for malignant ventricular arrhythmias associated with rociletinib-induced QT prolongation along with the complex physiologic interplay between electrolyte imbalances, hyperglycemia, insulin therapy, and pause-induced repolarization changes. To the best of our knowledge, this is the first published case report of TdP and macroscopic T-wave changes associated with rociletinib.

The normal repolarization time of the His-Purkinje conduction system is determined by the preceding diastolic interval, where longer periods of refractoriness result after pauses. Technically, electrical alternans reflects variations with every other beat. In this case, small changes in diastolic interval from frequent PACs accentuated the lengthening of the following phase of repolarization.³ These dramatic changes in T-wave morphology and duration likely reflect increases in heterogeneity and dispersion of both His-Purkinje and myocardial refractoriness as the surface

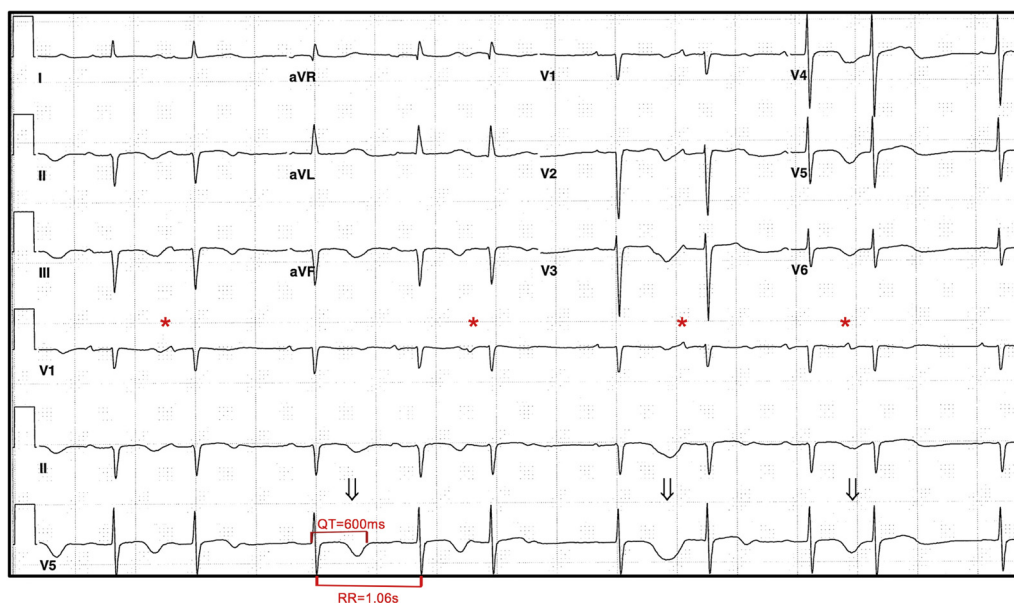


Figure 1 Twelve-lead electrocardiogram at presentation demonstrating macroscopic T-wave changes, with most pronounced abnormalities after premature atrial contraction–induced pauses. Corrected QT interval by the Bazett formula is 582 ms. Asterisks indicate premature atrial contractions and arrows indicate T-wave changes.



Figure 2 Premature ventricular contractions with R-on-T phenomenon during deeply inverted T-wave prolongation and initiation of torsades de pointes.

T wave is predominantly composed from the latter. We postulate that the frequent atrial ectopy in this case likely contributed to increased arrhythmogenicity.

Although the mechanism behind TKI-associated QT prolongation is unclear, 2 main theories of direct and indirect effects have been postulated. First, the 3-dimensional structure of the drug may lead to binding to the human ether-a-go-go-related gene potassium ion channels (hERG K⁺).⁴ hERG regulates the IKr channels, which contribute to the delayed rapid outward movement of K⁺, and thus repolarization of

the cell. There are multiple hERG binding sites that various QT-prolonging drugs have been shown to effect. Additionally, more indirect effects of TKIs may be attributed to the interactions with other QT-prolonging medications.⁵

We speculate that the current clinical presentation was a “2-hit” scenario with TKI-induced QT prolongation and secondary exacerbation from drug-induced hyperglycemia and subsequent treatment with insulin. Importantly, TdP was exacerbated after intravenous insulin was initiated. Although data are limited, studies have shown significant

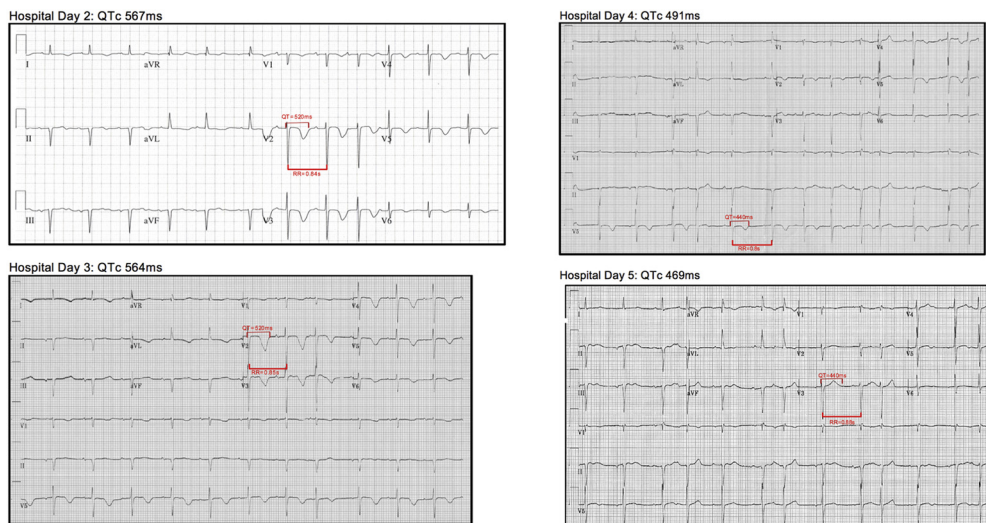


Figure 3 Gradual improvement in corrected QT interval prolongation and macroscopic T-wave changes on hospital days 2 through 5.

influences of glycemic milieu and insulin therapy on QT prolongation. Pickham and colleagues⁶ reviewed data from 940 patients and found a nearly 4-fold risk of QTc prolongation in those with glucose greater than 180 mg/dL compared to less than 140 mg/dL. They hypothesized that hyperglycemia results in overproduction of reactive oxygen species that target the IKr ion channels directly. Gastaldelli and colleagues⁷ studied 35 nondiabetic patients and found that insulin infusions prolonged QTc intervals within 30 minutes of administration. This was attributed to insulin-induced hyperpolarization via stimulation of sodium potassium ATPase in addition to increasing norepinephrine levels, both of which result in increased cellular potassium uptake. This shift of transcellular potassium gradient inward leads to further reduction of IKr channels and thereby QT prolongation. As a late-coupled premature ventricular contraction produced this phenomenon, it is likely that an interaction between multiple ion channels may have been involved, rather than an isolated acquired IKr abnormality. The presence of borderline QT prolongation at baseline of 450 ms may have indicated a subclinical mutation.

Based on electrolyte shifts that are potentiated from an adrenergic pathway and the effect of insulin on sodium potassium pumps, prophylactic management with beta-blockers and/or potassium and magnesium replacement may prevent the complication observed in this case report. In a study by Robinson and colleagues,⁸ concomitant potassium infusion during intravenous insulin therapy decreased QT dispersion

and beta-blockers were found to significantly reduce QTc and QT dispersion prolongation. Alternatively, intravenous insulin therapy could have been withheld in the absence of significant acidosis and hyperglycemia-related sequelae in this case.

This presentation of QT prolongation and macroscopic T-wave changes in a patient on rociletinib highlights the importance of routine electrocardiographic monitoring and further investigation to better understand the complex interplay between hyperglycemia and abnormalities in repolarization.

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