FELLOWS CORNER

A case series of drug-induced torsades de pointes in patients on multidrug-resistant tuberculosis treatment: Beware the gift that conceals a blade

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Introduction

Effective treatment of multidrug-resistant tuberculosis (MDR-TB) requires a combination of multiple drugs administered for an adequate duration,[1] which alone or in combination can cause prolongation of QTc. The incidence of arrhythmia has traditionally been considered low.[1,2] The current case series describes 5 patients on MDR-TB treatment presenting with documented/presumed torsade de pointes (TDP).

Case 1

A 42-year-old woman with a known case of pulmonary tuberculosis on an MDR regimen (Supplemental Table 1) presented with complaints of multiple episodes of vomiting and syncope. She had well-controlled hypertension and type 2 diabetes mellitus, and was post coronary artery bypass grafting for atherosclerotic coronary artery disease on optimal medical management. In the emergency room, 12-lead electrocardiography (ECG) was done (Figure 1). Subsequent ECG showed presence of short run of TDP secondary to QT prolongation (Supplemental Figure 1). This patient was put on temporary pacing wire with the pacing rate at 110 beats/min. Laboratory reports showed hypokalemia with K^+ of 2.2 mEq/L. The patient was maintained at potassium >4.0 mEq/L and magnesium >2.0 mg/dL and a pacing rate of 110 beats/min. Unfortunately, the patient died of type 2 respiratory arrest 2 weeks after the admission despite the supportive measures.

Case 2

A 45-year-old woman with a known case of cavitary pulmonary TB on an MDR regimen presented with discomfort in the chest and episodes of severe nausea and vomiting, and was referred to us in view of ST-segment elevation myocardial infarction (MI) (Supplemental Figure 2A). The patient had taken intensive-phase treatment, during which she was given moxifloxacin 400 mg, bedaquiline 400 mg, linezolid 600 mg, clofazimine 100 mg, and cycloserine 500 mg once daily in the intensive phase, which was completed 2 weeks prior, and was currently in the continuation phase, on moxifloxacin 400 mg, linezolid 300 mg, clofazimine 100 mg once daily, cycloserine 250 mg twice daily, and pyridoxine 100 mg.

The patient was started on injection magnesium sulfate and potassium in view of TDP. After aggressive potassium and magnesium supplementation, the TDP was controlled. ECG in sinus rhythm showed QT prolongation with pickelhaube sign with widespread T-wave inversion (Supplemental Figure 2B). The patient was monitored for recurrence of cardiac arrhythmia, which did not recur. The patient subsequently discharged with a magnesium level of >2 mg/dL and potassium level >4 mEq/L with advice to stop moxifloxacin and frequent monitoring of ECG.

WHAT WE LEARNED FROM THIS CASE

- In patients with multidrug-resistant tuberculosis, there is a risk of developing torsade de pointes, especially in patients who are on multiple QT-prolonging drugs.
- The recognition of this risk of torsade de pointes is especially important in times of fluid shifts (eg, diarrhea, vomiting) and electrolyte imbalances (hypokalemia, hypomagnesemia).
- Increased vigilance and electrocardiographic monitoring is required in such patients of multidrug-resistant tuberculosis on multiple QT-prolonging drugs.

KEYWORDS Torsade de pointes; Multidrug-resistant tuberculosis; Bedaquiline; Drug-induced QT prolongation (Heart Rhythm O2 2024;5:324–326)

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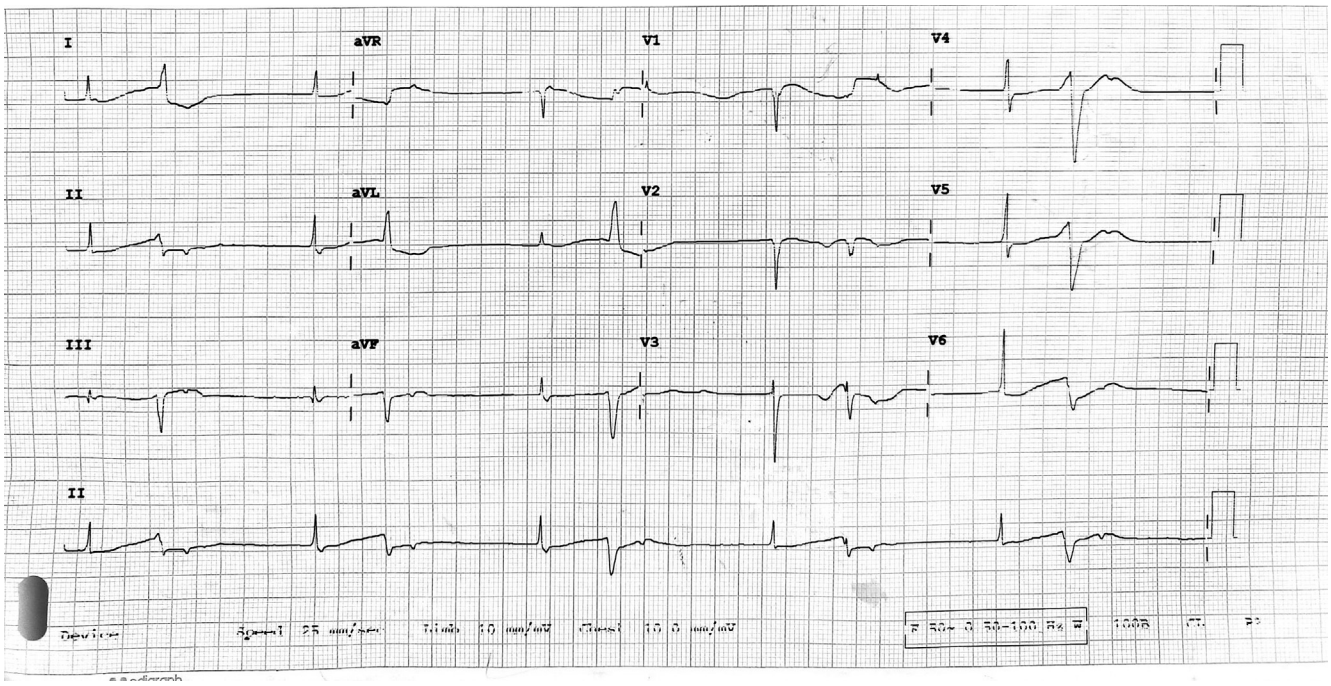

Figure 1 Electrocardiography showed sinus bradycardia, junctional escape rhythm, and QT prolongation >600 ms with early afterdepolarization–triggered premature ventricular complexes.

Case 3

A 60-year-old woman with a known case of sputum-positive TB presented with an episode of syncope to the emergency. During the past 15 days, she also had episodes of presyncope, nausea, and vomiting. This patient was a known case of sputum-positive MDR pulmonary TB resistant to isoniazid, rifampicin, and second-line injectables. The patient had intermediate sensitivity to moxifloxacin. She was started on bedaquiline 400 mg once daily for 14 days, which was completed 1 week prior, and was currently on bedaquiline 200 mg on alternate days, linezolid 600 mg once daily, clofazimine 100 mg once daily, cycloserine 100 mg twice daily, and delamanid 100 mg twice daily.

In emergency room, 12-lead ECG was done (Supplemental Figure 3). The ECG shows macroscopic T-wave alternans with QT prolongation and the beginning of a short run of TDP at the end of the rhythm strip. Potassium report from the laboratory was normal (4.1 mEq/L). However, the patient refused admission despite counseling about the high risk of ventricular tachycardia and sudden cardiac death.

Case 4

A 44-year woman presented to the emergency room with episodes of giddiness and syncope for the prior 3 days. She was a known case of MDR pulmonary TB, currently in the continuation phase on moxifloxacin 400 mg once daily, bedaquiline 200 mg thrice weekly, linezolid 600 mg once daily, clofazimine 100 mg once daily, and pyridoxine 100 mg once daily.

ECG done in the emergency room showed presence of TDP (Supplemental Figure 4). In view of the laboratory findings indicating hypokalemia, intravenous administration of potassium, with magnesium, was employed to restore potassium levels above 4.0 mEq/L and magnesium levels exceeding 2.0 mg/dL. After stabilization in the emergency room, the patient was advised admission to the intensive care unit; however, the patient and the relatives declined further stay at the hospital.

Case 5

A 22-year-old man was admitted with complaints of easy fatiguability and pedal edema in the prior week. The patient was a known case of cervical lymphadenopathy, secondary to MDR-TB on treatment (Supplemental Table 1). The ECG at presentation in the emergency room showed presence of QT prolongation, with macroscopic T-wave alternans (Supplemental Figure 5). This patient collapsed suddenly and could not be revived despite resuscitative attempts.

Discussion

The World Health Organization framework for monitoring adverse drug safety emphasizes the potential need for ECG, anticipating future regimens with 2 or 3 agents that could prolong the QT interval.[1] However, the use of ECG for monitoring the QT interval in real-world practice in these patients is low. In a California study, <10% of patients in the cohort had ECGs performed at all 6 predesignated time points.[2] This case series describes 5 patients on an MDR regimen who presented with TDP. Of these patients, 3 had vomiting episodes that contributed to the development of hypokalemia and subsequent QTc prolongation. All of these patients were on at least 2 QTc-prolonging drugs.

With respect to the reported cases in published trials, drug-related cardiac arrhythmias and fatality are considered rare. In the endTB observational study, 2 fatal drug-related cardiac events and 1 drug-related cardiac arrhythmia were documented, "all associated with hypokalemia and involving the use of bedaquiline, clofazimine, capreomycin, and p-aminosalicylic acid (excluding moxifloxacin or delamanid)."[1,3] The DELIBERATE trial (Evaluating the Safety, Tolerability, and Pharmacokinetics of Bedaquiline and Delamanid, Alone and in Combination, For Drug-Resistant Pulmonary Tuberculosis) reported no grade 3 or 4 QT adverse effects.[4]

Patients at risk or with prolonged QT intervals were excluded from TB-PRACTECAL (Pragmatic Clinical Trial for a More Effective Concise and Less Toxic MDR-TB Treatment Regimen(s)) and ZeNix (Various Doses and Durations of Linezolid Plus Bedaquiline & Pretomanid in Participants With Drug Resistant Tuberculosis)trials.[4,5] These include those with a QTc interval by Fridericia's formula exceeding 500 ms, a history of cardiac disease, syncopal episodes, significant arrhythmias, congenital QT prolongation, TDP, or cardiomyopathy.

The half-lives of bedaquiline and its N-monodesmethyl metabolite are 6 months and 5.5 months, respectively. Due to its long life, bedaquiline remains in the body beyond the duration of its use, and this factor must be borne in mind while interpreting the QT prolongation in patients who are not taking bedaquiline concurrently.[6]

This case series underscores the importance of awareness regarding adverse effects of a multidrug regimen for antituberculosis therapy. The QTc-prolonging effects of these drugs become especially important during the times of fluid shift and electrolyte imbalances. Increased caution and monitoring should be done to prevent QTc prolongation during these times particularly in patients with multiple QT-prolonging drugs, and to prevent potentially fatal effects of the therapy.

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