A Woman with Tuberculosis Multidrug Resistance and QTc Prolongation Repetitive Interval: A Case Report

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Abstract

Background : Prolonged QTc interval is one of the side effects of the short-regimen MDR-TB. QTc prolongation is a risk factor for Torsades de pointes and is influenced by many factors. **Case** : 47-year-old woman who was diagnosed with MDR-TB through GeneXpert examination and received short-regimen MDR-TB. This patient experienced repeated QTc prolongation, with peak QTc interval 600 msec occurring at 4th month with mild hypokalemia without clinical symptoms. The patient completed 9 months of short-regimen therapy with improve chest x ray followed by negative sputum culture. **Conclusion** : Short-regimen MDR-TB contains several drugs that cause QTc prolongation. Clinical evaluation is required in patients with QTc prolongation before changing the regiment.

Keywords*: TB-MDR, QTc prolongation, Moxifloxacin*

Introduction

Multidrug-resistant tuberculosis (MDR-TB) is still a world health problem and a threat to TB control globally. WHO estimates that there are about 3.3% new MDR TB cases and 20% MDR TB re-treatment cases. Several factors that contribute to the spread of MDR-TB, especially in endemic areas, include limited treatment options, high costs, ineffective and prolonged therapy. In 2016 WHO announced a short-term regimen for MDR-TB therapy that is expected to reduce costs, reduce costs and be effective for MDR-TB patients worldwide. This regimen consists of kanamicin, moxifloxacin, etionamide, clofazimin, pyrazinamide and high doses of INH for 4-6 months of the intensive phase and is followed by a follow-up phase consisting of moxifloxacin, clofazimin, pyrazinamide and ethambutol for 5 months [1, 2].

Although the short-term MDR-TB regimen brings new hope, this cannot be separated from the side effects caused by some MDR-TB drugs, one of which is the lengthening of the corrected QT (QTc) interval. QTc prolongation is a risk factor for the incidence of Torsades de Pointes (TdP) as well as arrhythmias that have the

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potential to cause death. According to a review study the prevalence of sudden death due to TdP due to QTc prolongation due to MDR-TB drugs may be less than 1%. Electrocardiogram (ECG) monitoring is required in MDR-TB patients receiving short-term therapy, but in resource-limited areas this is neither a limitation nor a condition of using short-term MDR-TB regimens [2, 3].

The QT interval is the portion of the EKG that is calculated from the start of the QRS complex to the end of the T wave, it describes the time it takes for the ventricular myocardium to depolarize and repolarize or the time it takes the myocardium to replenish between heartbeats measured in seconds (s) or milliseconds (ms). The QT interval is influenced by heart rate, which can shorten at a fast heart rate and lengthen at a slow heart rate so the QT interval needs to be corrected. The QT or QTc correction formula is needed to estimate the QT interval at a heart rate of 60 times a minute. The normal value of QTc in men <450 ms and in women <470 ms [4, 5].

Fluoroquinolones (FQ) are one of the most effective mycobactericidal classes. FQ has also been noted to cause prolongation of QTc and TdP especially in the elderly population. All FQ can be used for MDR-TB treatment including Levofloxacin (Lfx) and Moxifloxacin (Mfx). Mfx was noted to be the FQ that caused more QTc lengthening than the other FQs (5, 6). Based on the above description we are interested in reporting a recurrent case of MDR TB and QTc prolongation interval in a woman.

Case Presentation

A 47-years-old woman with a previous history of failure to treat category 1 OAT was diagnosed with rifampicin-resistant pulmonary TB by geneXpert examination. The results of the x-ray examination obtained the results according to figure 1. Patients received MDR TB therapy including Kanamicin (Km) 750 mg, moxifloxacin (Mfx) 600 mg, clofazimine (Cfz) 100 mg, Ethionamid (Eto) 500 mg, isoniazid (H) 600 mg, pyrazinamide (Z) 1500 mg and ethambutol (E) 800 mg. Before starting therapy, the patient was previously carried out a baseline examination, including a complete laboratory examination, electrocardiogram (EKG), audiometry and psychology.

After receiving therapy for 1 week the patient experienced prolonged QTc interval 545 msec, without laboratory abnormalities or clinical symptoms. Mfx was stopped for 3 days and an EKG was evaluated every day. After the QTc interval returned to normal (411 msec), Mfx was started at a dose of 400 mg. A week later the QTc interval of 468 msec and Mfx was again given at a dose of 600 mg while evaluating the ECG (Figure 2 & Table 1).

When entering the advanced stage of therapy, the patient again experienced a prolonged QTc interval of 600 msec so that Mfx was temporarily stopped and a laboratory evaluation was carried out. The laboratory results at that time showed that the patient had mild hypokalemia with a potassium value of 3.2 mmol/l. After correction of hypokalemia the QTc interval returns to normal and Mfx is started again at a dose of 200 mg for 7 days, and then continued at a dose of 400 mg until the end of therapy.

Entering the 7th month of therapy, the patient again experienced a prolonged QTc interval of 539 msec, without clinical symptoms and laboratory abnormalities (potassium 3.7 mmol/l). Currently Mfx is still given at a dose of 400 mg but the Cfz dose is reduced to 50 mg/day. After a week of evaluation the QTc returned to normal and Cfz was again given at a dose of 100 mg/day until the end of treatment. The patient had conversion of Acid-fast bacilli at 4th month followed by negative sputum culture until the end of therapy. The patient experienced clinical and radiological improvement, at the seventh month the treatment was completed and the patient was declared cured.

Table 1. QTC Serial

Time	QTc interval	Action
2nd week	545 msec	Mfx temporary stop
1st month	468 msec	Mfx 600 mg
2nd month	471 msec	Mfx 600 mg
4th month	600 msec	Mfx temporary stop
4th month	443 msec	Mfx 200 mg
5th month	491 msec	Mfx 400 mg
7th month	539 msec	Mfx 400 mg + Cfz 50 mg
7th month	433 msec	Mfx 400 mg + Cfz 100 mg

Table 2. Risk factors for QTc prolongation and torsades de pointes

Baseline and unmodified predisposition	Acquired risk factors : clinical condition
- Underlying conduction abnormalities (subclinical long QT syndrome) : genetic predisposition, family history of sudden death - Bradycardia - Female sex - Advanced age (linearly increased risk after 60 years)	- Electrolit imbalance : hypokalaemia, severe hypomagnesaemia, hypocalcaemia - Structural and functional heart problems : recent conversion from atrial fibrilation, ischaemic and congestive heart disease, ischaemic cardiomyopathy, dilated or hypertrophic congestive heart disease, congestive heart failure - Frequent conditions of TB patients : HIV infection, low BMI (malnutrition, starvation, and wasting syndrome), severe vomiting and diarrhea creating low potassium levels - Impaired renal function - Impaired hepatic funtion - Hypothyroidism

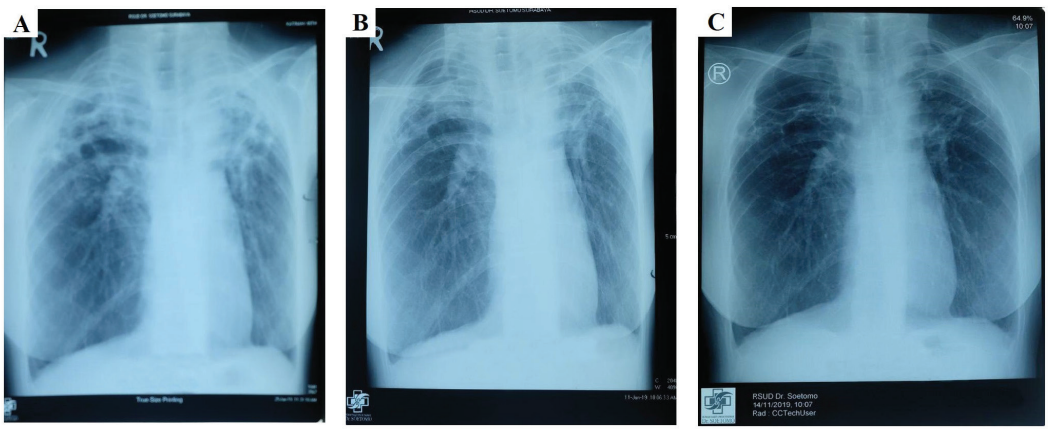

Figure 1A. Chest X-Ray at baseline; B. Chest X-Ray after 6 month therapy; C. Chest X-Ray end of therapy

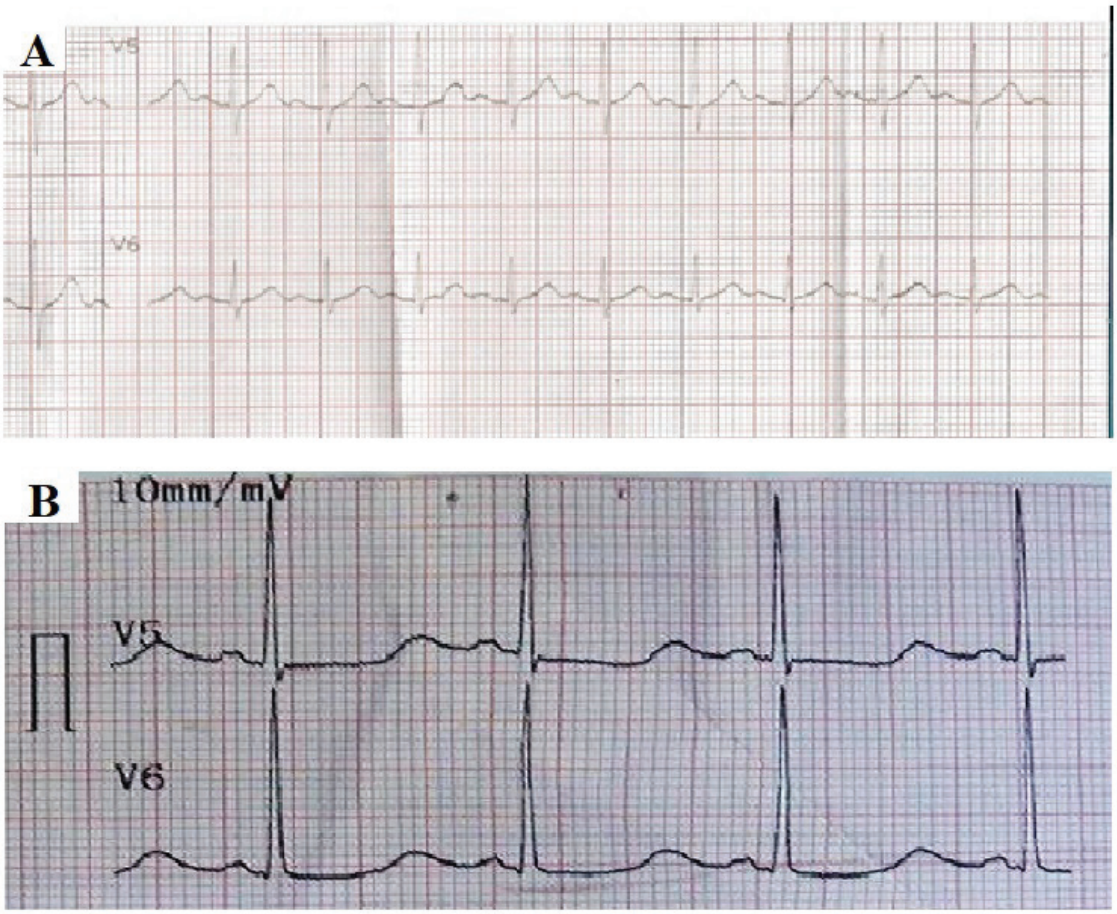

Figure 2A. ECG baseline with QTc 398 Msec; B. ECG after 4th month therapy with QTc 600 Msec.

Discussion

Prolonged QTc interval greater than 500 msec is generally thought to increase the risk of developing TdP in the majority of the group with congenital long QT syndrome. The risk of TdP or sudden death is not always directly related to the length of the QT interval or the duration of QTc prolongation during therapy, but it can still be influenced by many factors. Drug-induced QTc prolongation has different properties from drug to drug. All FQs were noted to cause QTc prolongation, but according to case reports Mfx has the greatest risk of causing QTc prolongation[2, 3]. The risk of QTc prolongation with FQ will be higher if there are electrolyte abnormalities and the use of other drugs that cause QTc prolongation[5, 6]. In this case, when the patient experienced QTc lengthening of 600 msec, there was also mild hypokalemia (potassium 3.2 mmol/l). Apart from stopping Mfx we also provide potassium intake to the patient.

A 2018 Indian study involving 467 patients receiving the Mfx regimen after a 4-month evaluation did not show a significant increase in QTc. Although there were 5 patients who experienced prolonged QTc interval, Mfx had to be temporarily stopped and given again without experiencing a cardiac event. According to the study Mfx 400 mg daily given for 4 months did not cause prolonged QTc interval[7].

In a South Korean study of 373 MDR-TB or NTM-TB patients receiving Mfx, Cfz and macrolide therapy, significant QTc prolongation occurred in 16.7% of patients with a maximum QTc value of 451 msec and a mean QTc lengthening of 33.6 msec from baseline.

This study concluded that drug combinations that cause QTc changes in MDR-TB or NTM therapy are generally safe to use[8]. Although Mfx significantly caused QTc prolongation it was of moderate duration with a mean increase of 4% in the therapeutic dose of 400 mg. The effect of Mfx on ventricular repolarization occurs primarily at times of maximum plasma concentration, but QTc prolongation may be decreased with repeated administration, therefore the risk of TdP is small at 400 mg/day[9]. In this case, QTc prolongation still occurred in the advanced phase of therapy even though Mfx had been given at a dose of 400 mg/day, this might occur because the patient was still receiving other drugs that caused QTc interval lengthening, which is Cfz. After receiving low dose Cfz (50mg/day), QTc returned to normal. Although the evidence is limited, Cfz has been noted to increase QTc interval between 10-20 msec[10].

Apart from FQ, there are several antibiotics used in MDR-TB therapy that are associated with prolongation of the QTc interval, such as bedaquilin, delamanid, and Cfz. The safety of using Mfx together with any of these drugs in MDR-TB therapy requires further clinical evaluation (Table 2). Until now, the incidence of TdP in clinical trials of TB patients is very rare, because the field conditions are difficult to evaluate for cardiotoxicity[10]. One study showed that the risk of Mfx-associated QTc prolongation was increased in individuals with certain genotypes[11].

Conclusion

QTc prolongation is one of the side effects of the short-term MDR-TB regimen. This can be related to several factors, including the combination of several drugs that cause QTc prolongation, and certain clinical conditions, especially electrolyte disturbances. Although the incidence of TdP associated with QTc prolongation in MDR-TB therapy is rare, ECG evaluation in patients receiving short-term MDR-TB therapy is needed. Therefore a clinical evaluation should be carried out in patients experiencing QTc prolongation before stopping or changing their MDR-TB treatment regimen.

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