Prolong QTc Interval in Ethionamide-Induced Hypothyroidism in the Treatment of Multidrug Resistant Tuberculosis (MDR TB)

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ABSTRACT

Background. Ethionamide, as part of multidrug resistant tuberculosis (MDR TB) treatment, is an antibiotic classified by WHO as a second-line drug with bactericidal property. Administration of ethionamide therapy is associated with the incidence of hypothyroidism in MDR TB patients. The resulting hypothyroidism can be a factor that triggers QTc interval prolongation on electrocardiogram (ECG) during anti-tuberculosis treatment

Case Presentation. A 77-year-old man with a history of pulmonary TB treatment one year ago, returned to undergo the intensive phase of pulmonary TB treatment for two months. Sputum evaluation at the end of the phase showed positive smear results, and the patient was diagnosed with MDR TB after further examination. Before starting MDR TB treatment, an initial ECG examination (QTc interval 0.41 seconds), TSH, and FT4 level were found to be within normal limits. MDR TB regimen including ethionamide 750 mg/day was given for the treatment. In the third month of treatment, the patient was diagnosed with hypothyroidism suspected to be related to ethionamide. In the seventh month of treatment, the patient complained of sudden weakness and QTc interval prolongation in the ECG (0.48 seconds). Ethionamide was stopped and the ECG was evaluated. No QTc interval prolongation was found after stopping ethionamide.

Conclusion. This case emphasizes the importance of monitoring side effects arising from anti-tuberculosis treatment, especially ethionamide. Accuracy in diagnosing and following up the side effects of ethionamide administration in MDR TB patients is necessary to prevent worse cardiac events.

Keywords. Ethionamide, QTc interval, hypothyroidism, MDR TB

ABSTRAK

Latar Belakang. *Etionamid sebagai bagian pengobatan* multidrug resistant tuberculosis *(MDR TB), adalah antibiotik yang diklasifikasikan oleh WHO sebagai obat lini kedua yang memiliki sifat bakterisida. Pemberian terapi etionamid berkaitan dengan kejadian hipotiroid pada pasien MDR TB. Hipotiroid yang terjadi dapat menjadi faktor yang mencetuskan pemanjangan interval QTc pada gambaran elektrokardiografi (EKG) selama pengobatan tuberkulosis*

Presentasi Kasus. *Laki-laki 77 tahun, diketahui sebagai penderita TB yang menjalani pengobatan 1 tahun yang lalu, telah menjalani pengobatan selama 2 bulan, dilakukan evaluasi BTA sputum dengan hasil positif. Dilakukan pemeriksaan lebih lanjut dan pasien didiagnosis MDR TB. Dilakukan pemeriksaan EKG awal (interval QTc 0.41 detik) dan pemeriksaan TSH dan FT4 didapatkan dalam batas normal. Diberikan pengobatan MDR TB termasuk didalamnya etionamid 750 mg/ hari. Bulan ketiga pengobatan, pasien diagnosis menderita hipotiroid yang diduga terkait etionamid. Pada bulan ketujuh pengobatan pasien mengeluh tiba-tiba lemas memberat, didapatkan pemanjangan interval QTc pada gambaran EKG (0.48 detik). Etionamid dihentikan dan dilakukan evaluasi gambaran EKG. Tidak ditemukan lagi pemanjangan interval QTc setelah penghentian etionamid.*

Kesimpulan. *Kasus ini menekankan pentingnya pemantauan akan efek samping yang timbul dari pengobatan anti tuberkulosis khususnya etionamid. Ketepatan dalam mendiagnosis dan menindaklanjuti efek samping pemberian etionamid pada pasien MDR TB diperlukan untuk mencegah kejadian kardiak yang lebih buruk.*

Kata Kunci. Etionamid, interval QTc, hipotiroid, MDR TB

INTRODUCTION

Multidrug resistant tuberculosis (MDR TB) has become a public health problem that has received global attention due to the morbidity and mortality it causes. The World Health Organization (WHO) reported that by 2016 there had been 10.4 million reported cases of pulmonary TB with estimated mortality of 1.3 million deaths in HIV-negative TB and 340.000 deaths in HIV-positive TB. Approximately 490.000 of the TB cases reported in 2016 were MDR TB with an additional 110.000 cases of isoniazid susceptible but rifampicin resistant (RR TB).[1] Detection, diagnosis and treatment of MDR TB is important to prevent further morbidity and mortality.

MDR TB treatment utilizes the MDR anti-tuberculosis drug guidelines which consist of 4 groups, including ethionamide as the second line drug. Ethionamide is a weak bactericide in TB treatment, can also cause hypothyroidism especially when combined with para-amino salicylic acid (PAS), but is reversible when drug administration is stopped.[2] Ethionamide has the same structure as methimazole, and has been shown to inhibit thyroid hormone synthesis and was reported to cause hypothyroidism in 1984.[3] Thyroid hormone deficit in hypothyroidism has cardiovascular effects with ECG manifestations of bradycardia, right bundle branch block (RBBB), inverted T, QRS prolongation, QT interval prolongation, infrequently ventricular arrythmia, *torsade de pointes*. Symptoms of hypothyroidism and its cardiac manifestations include dry skin, cold intolerance, weakness, constipation, decreased arterial pulse, hypotension, distant heart sounds, orthopnea and paroxysmal dyspnea.[4] Monitoring for cardiac symptoms and effects in the treatment of MDR TB is necessary to avoid poor patient outcomes.

CASE ILLUSTRATION

A 77-year-old man with a history of pulmonary TB treatment one year ago, returned to undergo the intensive phase of pulmonary TB treatment for two months. Sputum evaluation at the end of the phase showed positive smear results, and the patient was diagnosed with MDR TB after GeneXpert showed rifampicin resistant MTB. The patient was planned to receive second-line treatment. Before drug initiation, baseline thyroid function examination and ECG was carried out with normal result (FT4 1.15 mg/dl (1.00 - 1.70 mg/dl), TSH 2.75 μIU/ml (0.27 - 4.2 μIU/ml), ECG obtained showed normal sinus rhythm, heart rate 80 times/minute, normoaxis, inverted T in V1, and normal QTc interval 0.41 seconds (Figure 1).

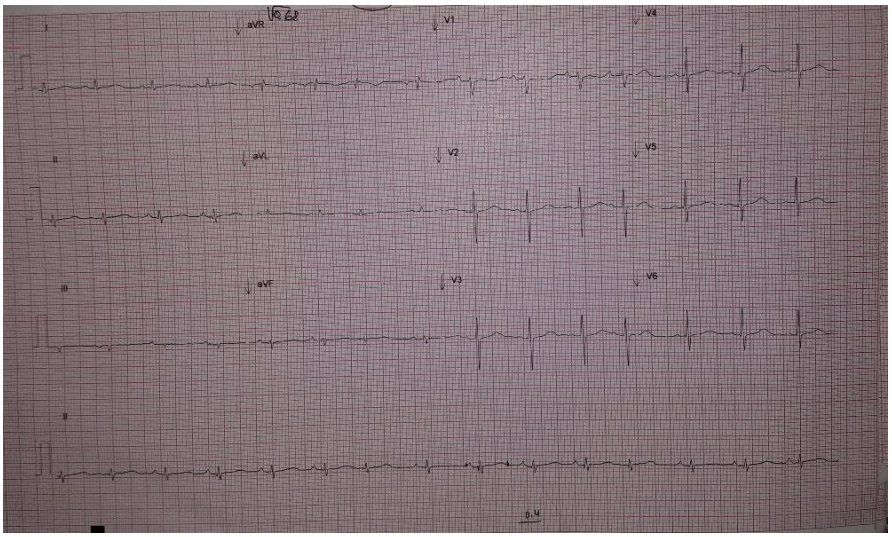

Figure 1. Baseline ECG before initiation of MDR TB therapy (normal QTc interval 0.41 seconds)

The patient began to receive MDR TB therapy consisted of per-oral isoniazid (INH) 800 mg once daily (OD), pyrazinamide 1000 mg OD, ethambutol 1000 mg OD, levofloxacin 625 mg OD, cycloserine 625 mg OD, ethionamide 750 mg OD, and PAS 4 gr OD. In the third month of the treatment, the patient complained of weakness. Blood pressure was 90/60 mmHg, pulse was 60 beat/min, breathing was 20 times/min, temperature was 36^{o} C, saturation was 99%, and laboratory evaluation showed marked changes in thyroid function (FT4 0.54 mg/dl and TSH 66.35 μIU/ml). The patient was diagnosed with hypothyroidism and given per oral levothyroxine 100 mcg OD. In the seventh month of treatment, the patient complained of sudden weakness, pulse evaluation was found to be 110 beat/min, then an ECG examination was performed with prolonged QTc interval (0.48 seconds) measured using Bazett's formula (Figure 2).

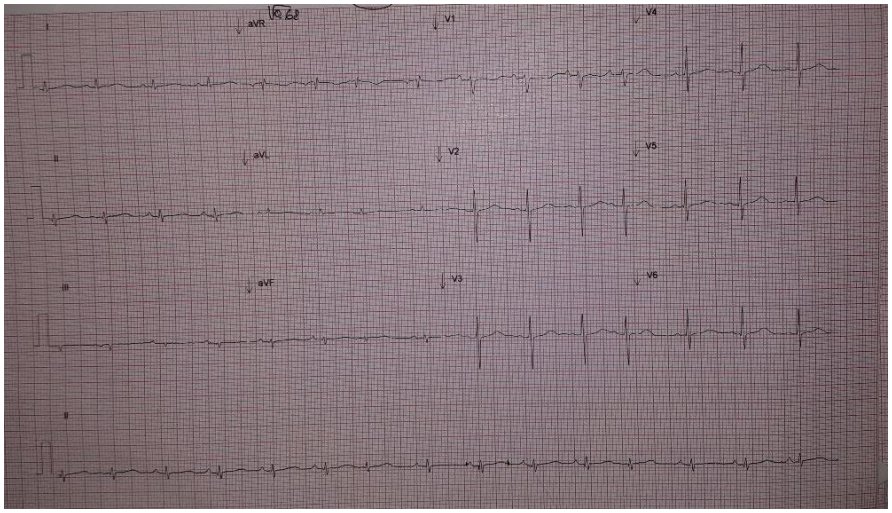

Figure 2. QTc interval prolongation 0.48 seconds after the seventh month of treatment (4 months after diagnosed with hypothyroidism)

Ethionamide was discontinued due to suspicion of ethionamide-induced QTc interval prolongation and ECG evaluation was performed every 24 hours. After the administration of ethionamide was stopped, the QTc interval returned within normal limits of <0.45 seconds (Figure 3-5).

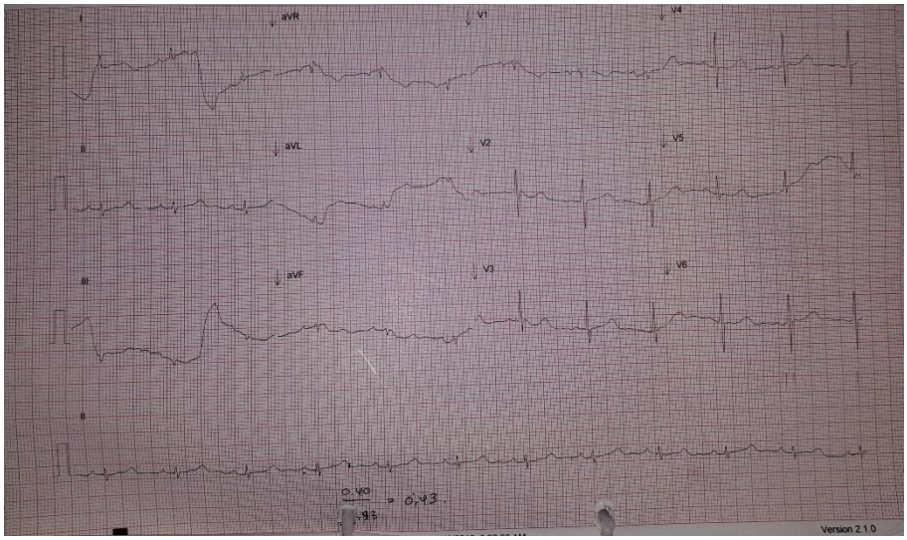

Figure 3. ECG evaluation showed QTc interval 0.43 seconds (first day of ethionamide discontinuation)

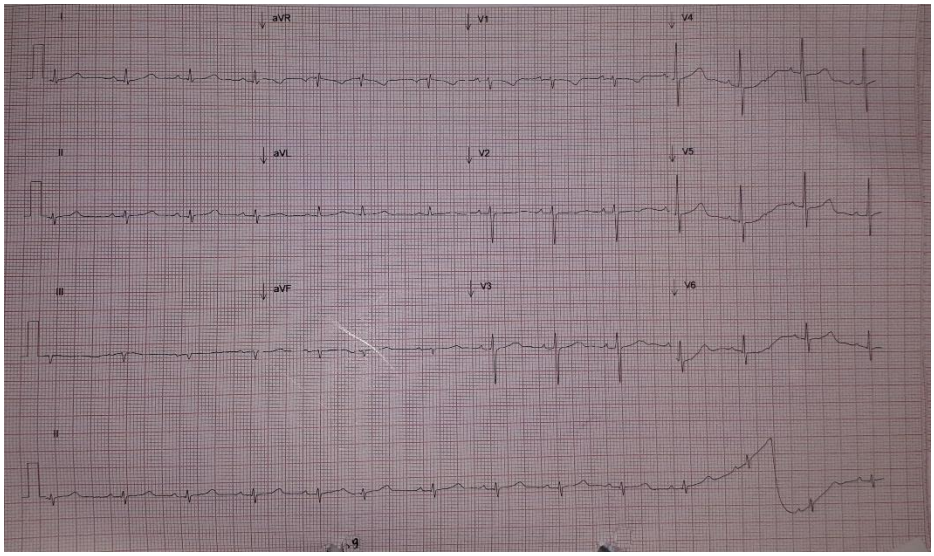

Figure 4. ECG evaluation showed QTc interval 0.41 seconds (second day of ethionamide discontinuation)

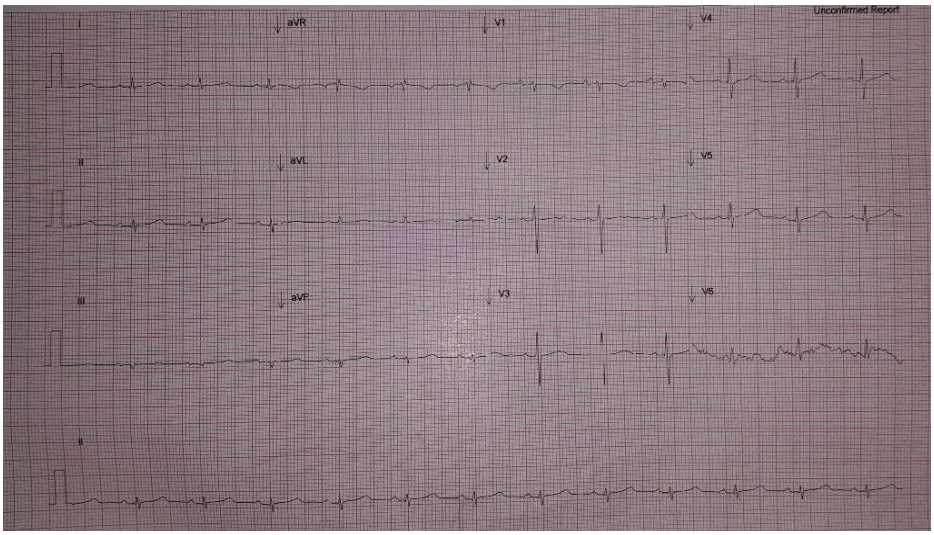

Figure 5. ECG evaluation showed QTc interval 0.40 seconds (third day of ethionamide discontinuation)

DISCUSSION

MDR TB treatment carries many side effects and risks. Side effects of MDR TB therapy include dysglycemia, QT interval prolongation, respiratory disorders, nephrotoxicity, peripheral neuropathy, optic neuropathy, ocular toxicity, skin rash, gastrointestinal disorders, hypothyroidism, psychiatric disorders, thrombocytopenia and anemia.[2] Hypothyroidism can be related to the administration of ethionamide by inhibiting thyroid hormone synthesis by blocking the organification and uptake of iodine into thyroid cells. During long-term therapy, hypothyroidism is common in adult and pediatric patients (20-70%).[5]

Hypothyroidism occurs due to reduced secretion of T_3 and T_4, as a consequence of damage to the thyroid gland itself. Thyroid hormone deficit affects the cardiovascular system and has a variety of cardiovascular manifestations, such as failure of cardiac contractility, decreased cardiac output, increased vascular resistance and cardiac electrical abnormalities, one of which can be seen from the ECG picture of QT interval prolongation. Because the cardiovascular system is one of the most important targets of thyroid hormones and is very sensitive to minimal binding of circulating thyroid hormones, the physiological chronotropic response and normal stress of the heart muscle in the diastolic phase depend on the expression of tri-iodothyronine in heart cells. QT interval prolongation indicates prolongation of ventricular repolarization, on the ECG measured from the beginning of the QRS complex to the end of the T wave. QT interval varies based on heart rate and must be corrected to QT corrected (QTc) which among others uses Bazzet's correction and one of the literatures mentions QTc interval prolongation occurs if the QTc interval is > 450 milliseconds.[4,6,7,8,9]

In most patients, QTc interval prolongation is asymptomatic, and can only be seen with routine ECG monitoring. Patients with arrhythmias and QTc interval prolongation may present with symptoms of dizziness, faintness, or syncope. QTc prolongation is a risk factor for torsade de pointes arrhythmia and sudden cardiac death.[9]

CONCLUSION

A 77-year-old man undergoing MDR TB treatment was reported with hypothyroidism-induced ethionamide after the third month of treatment and QTc interval prolongation was discovered in the seventh month. After discontinuing ethionamide and doing monitoring ECG assessments, the ECG result was reported to be improved, with no QTc interval prolongation. Monitoring for cardiac symptoms and consequences is essential in the treatment of MDR TB to avoid poor patient outcomes.

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