

## Atypical Arrhythmia Associated with Lithium Therapy: When to Expect the Unexpected?

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### INTRODUCTION

A 63-year-old patient experienced lithium toxicity, presenting with ventricular tachycardia (VT) due to up-titration of her lithium dosage, which was resolved with hemodialysis. Lithium has a narrow therapeutic window, with toxicity risk being higher in the elderly.<sup>1</sup> Lithium may cause direct myocardial toxicity that is reversible upon discontinuation.<sup>2</sup> Both benign and potentially life threatening electrocardiographic (ECG) changes have been reported, VT being a very rare occurrence.<sup>3</sup> Although there is no antidote for lithium toxicity, hemodialysis and intravenous (IV) hydration appear to have good therapeutic effects.<sup>4</sup>

### CASE

A 63-year-old woman presented with altered mental status, slurred speech, and abnormal gait. Her past medical history included diabetes mellitus, hypertension, hyperlipidemia, and bipolar disorder, for which she was treated with metformin, lisinopril, atorvastatin, and lithium (300 mg twice per day). Two weeks ago, the patient was admitted due to pneumonia and was treated with intravenous (IV) ceftriaxone and azithromycin. ECG showed normal sinus rhythm with incomplete right bundle branch block and a corrected QT interval (QTc) of 460

msec. Before discharge, lithium levels were found to be subtherapeutic (lithium level 0.5 mmol/L; normal 0.6 to 1.0 mmol/L) and the dosage was doubled to 600 mg twice per day. No repeat blood work was performed thereafter. Upon arrival via emergency medical services, ECG monitoring revealed monomorphic VT (Figure 1). The patient had no cardiovascular symptoms and was hemodynamically stable. Treatment was attempted in the ambulance with 150 mg IV amiodarone, with no effect. In the emergency department, stable monomorphic VT was still present, and a second attempt at treatment with 150 mg IV amiodarone was made, without any ECG changes. Cardiology was consulted and the patient was cardioverted with 200 J, resulting in conversion to baseline ECG, but with deep T wave inversion in the precordial leads and a prolonged QTc (554 msec) (Figure 2). Her lithium level was noted to be 1.8 mmol/L (toxic concentration > 1.5 mmol/L). The patient was transferred to the intensive care unit and started on emergent hemodialysis to remove lithium and to prevent the recurrence of monomorphic VT, which was considered to be secondary to lithium toxicity. No further episodes of VT appeared and the presenting symptoms resolved. To exclude other causes of ventricular arrhythmia, blood tests, transthoracic echocardiogram (TTE), and coronary angiogram were ordered. Electrolytes, renal, hepatic, and thyroid function tests were normal (potassium 4.2 mEq/L, blood urea nitrogen 20 mg/dL, creatinine 0.9 mg/dL, aspartate transaminase 22 U/L, alanine transaminase 25 U/L). TTE revealed normal ventricular wall size, motion, and systolic function (left ventricular ejection fraction 55-65%), and normal right heart and pulmonary artery pressures. No hemodynamically significant stenoses of the coronary arteries were observed. The patient did not develop any further episodes of VT during hospitalization, her QTc interval decreased (483 msec at discharge), and she was discharged with discontinuation of lithium.

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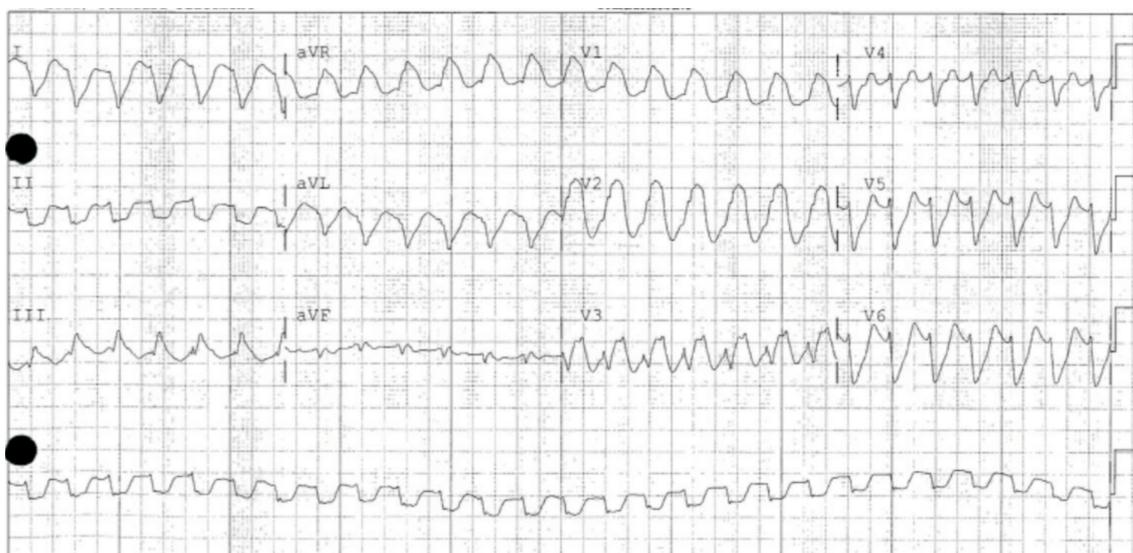


Figure 1. Electrocardiogram showing monomorphic ventricular tachycardia at a rate of 160 beats per minute.

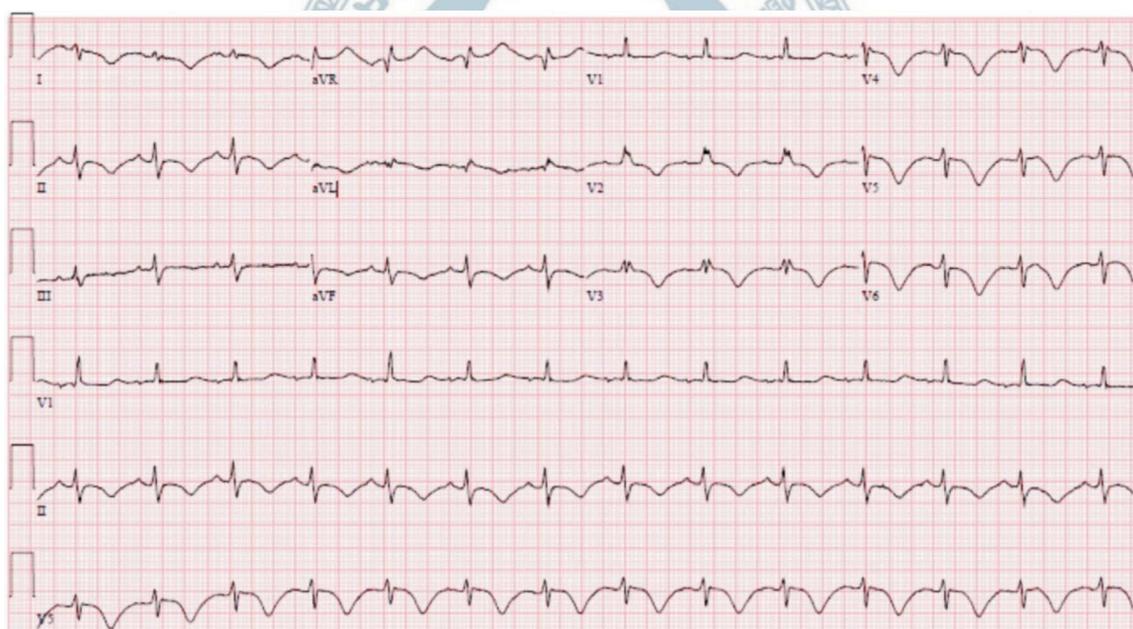


Figure 2. Electrocardiogram after electric cardioversion showing normal sinus rhythm at a rate of 80 beats per minute, right bundle branch block, deep T wave inversion in the precordial leads, and a prolonged corrected QT interval of 554 msec.

## DISCUSSION

Lithium has come a long way since its introduction as a treatment for gout in the 19<sup>th</sup> century, becoming the drug of choice for treating bipolar disorder for decades. Years of use have shed some light upon its mechanisms of action and side effects, but they are still not entirely understood. The pathophysiology by which lith-

ium affects the heart appears to be multifactorial. Leading theories suggest that lithium might cause electrical instability in both atria and ventricles by a dose-dependent inhibition of myocyte voltage-gated sodium channels that decreases intracellular potassium.<sup>5</sup> This potential mechanism explains why some of the ECG changes observed in patients on lithium resemble hypokalemia, despite normal potassium levels: depressed ST segments,

QTc prolongation, and presence of U waves. The potassium influx caused by lithium is not generally significant enough to decrease systemic potassium levels. However, in cases of susceptible individuals or in patients with cardiac Na/K channels that are particularly selective to lithium, the localized intracardiac hypokalemia could become clinically significant. Though no cause and effect relationship has been found between lithium and hypokalemia, treatment with potassium has been studied as a method of reducing lithium toxicity in animal models. Hypercalcemia and hypermagnesemia can also be caused by lithium therapy,<sup>1</sup> and these particular electrolyte imbalances have been associated with lethal tachyarrhythmias. Lithium can lead to direct myocardial toxicity as well, which is reversible upon discontinuation of the drug.<sup>2</sup> Cardiotoxicity is mainly noticed at serum lithium levels > 1.5 mmol/L, but can be precipitated by rapidly changing concentrations.<sup>6</sup>

Lithium treatment can induce ECG changes in both therapeutic and toxic doses.<sup>3</sup> Some of the most commonly reported ECG patterns are T-wave depression and sinus node dysfunction, which are mostly benign and asymptomatic. Sinoatrial block, intraventricular conduction delay, ST depressions or elevations, the Brugada pattern, atrioventricular conduction delays, and QTc prolongation are also seen. The latter ECG changes can result in ventricular instability, cardiac arrhythmias, and sudden cardiac death, although ventricular tachycardia is rarely reported in association with lithium so far.<sup>3</sup>

ECG changes are dependent on both duration of treatment and the serum lithium levels, therefore it is important to frequently monitor patients to ensure safe use. However, there are no standardized guidelines for serial ECG monitoring in patients on lithium therapy. A baseline ECG with routine periodic ECGs and serum lithium levels should be obtained, with frequency dependent on the severity of comorbidities.

There have been studies suggesting that older adults require decreased lithium doses, even in those who are on chronic lithium therapy.<sup>7</sup> Normal aging processes explain this need, because of the physiologic reduced renal function and decline in water volume.<sup>8</sup> Furthermore, the lithium serum concentration leading to toxicity may be lower than that of younger patients.<sup>9</sup> Another issue in the elderly is the presence of more medical comorbidities with various concomitant medications, increas-

ing the risk of potential drug interactions. Studies suggest that the elderly should be monitored more carefully while on lithium therapy, with regular electroencephalogram, ECG, and thyroid and renal function tests, as toxicity may occur even when the serum lithium concentration is within normal range.<sup>10</sup>

Lithium is a challenging drug to manage, due to its narrow therapeutic index and concern for toxicity. Although non-invasive therapies, such as IV fluids, magnesium sulfate, or antiarrhythmic medication may be useful, treatment of lithium overdose with hemodialysis is recommended in the presence of life-threatening dysrhythmias, regardless of serum lithium levels.<sup>4</sup>

## LEARNING POINTS

Lithium, with its narrow therapeutic window, might increase cardiac arrhythmogenicity despite normal and toxic doses. While ventricular tachycardia is a rare side effect of lithium toxicity, the ECG changes caused by lithium overdose are similar to those seen in worsening hypokalemia. The current gold standard in the treatment of lithium overdose is hemodialysis, but other less invasive therapeutic approaches could prove useful in the treatment of associated ventricular tachycardia. There is a need for more in-depth studies regarding the arrhythmic effects of lithium.

## DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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