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CARDIAC ARRHYTHMIA SPOT LIGHT

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Pueraria mirifica, an estrogenic tropical herb, unveiled the severity of Type 1 LQTS caused by *KCNQ1*-T587M

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1 | INTRODUCTION

One-third of patients with apparent acquired long QT syndrome (LQTS) carry a mutation in, at least, one of the three major LQTS-related genes including *KCNQ1*, which is responsible for type 1 LQTS.[1] We here report a case of acquired LQTS carrying a *KCNQ1*-T587M mutation,[2-4] which presented a very severe phenotype triggered by *Pueraria mirifica*. The compound is derived from a tropical plant containing estrogen-like substances and potentially modifies cardiac repolarization.[5-7]

2 | CASE REPORT

A 24-year-old woman developed sudden onset of pre-syncope while she was resting at home during the daytime and called emergency medical services. In the ambulance, she collapsed and ventricular fibrillation (VF) was detected. Immediate electrical shock terminated VF. Upon arrival at the hospital, her ECG showed a marked QT prolongation (corrected QT [QTc] = 674 ms) and notched T waves (Figure 1A). Her laboratory examination showed no electrolyte abnormality (K: 3.8 mEq/L, Ca: 8.9 mg/dL, Mg: 1.7 mg/dL). Soon after her arrival, we injected magnesium sulfate. There was neither medical history of syncope nor family history of cardiac disease or sudden death. Further history taking revealed that she had been taking *Pueraria mirifica*, an estrogenic herb containing miroestrol and deoxymiroestrol, for a week before hospitalization without any other QT prolonging agents. Her menstrual cycle was regular, and the event occurred 7 days before her menstruation (luteal phase). After admission, the estrogen supplement was discontinued.

On day 2, her ECG still presented prolonged QTc interval (QTc = 764 ms) (Figure 1B) and she developed repetitive torsade de pointes (TdP) on emotional agitation (Figure 2A). After oral mexiletine (300 mg/kg/d) was started, QTc interval shortened to 631 ms, but TdP was not completely suppressed. A total of 14 electrical shocks were required. Mild conscious sedation finally suppressed the TdP storms. QTc gradually shortened, and on day 4, mexiletine and sedation were discontinued (QTc = 544 ms). On day 8, QTc interval further shortened to 439 ms (Figure 2B). Epinephrine stress test[8] was conducted and revealed drastic QTc prolongation from 491 to 683 ms with marked T-wave abnormality (Figure 3A,B).

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After obtaining the informed consent for genetic analysis approved by our institutional review board, we performed screening for *KCNQ1* and *KCNH2* by denatured high-performance liquid chromatography (WAVE system; Transgenomic Omaha) in addition to the analysis including all LQTS-related genes using HaloPlex HS custom panel (Agilent Technology)[9] and identified a heterozygous *KCNQ1* variant: c.1760C>T:p.Thr587Met (T587M). There were no pathogenic variants in other genes. Her relatives did not consent for genetic testing. After taking bisoprolol (0.06 mg/kg/d), she still presented marked QT prolongation during exercise. Considering her high risk of arrhythmia, we implanted an ICD after a careful discussion with the patient.

Five years after the first event, the patient has been free from recurrence of arrhythmic events.

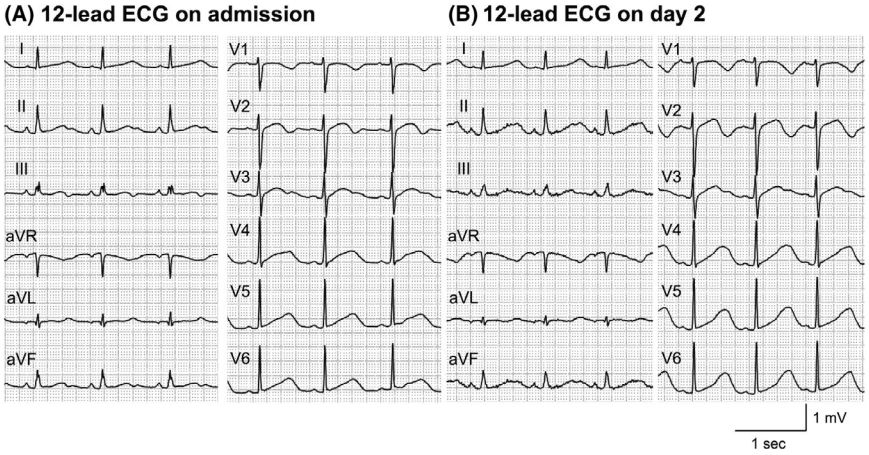

FIGURE 1 Twelve-lead surface ECGs of the patient. A, ECG on admission showing long QT interval. The corrected QT interval (QTc) = 674 ms. (B) ECG on day 2 after admission. QTc = 764 ms

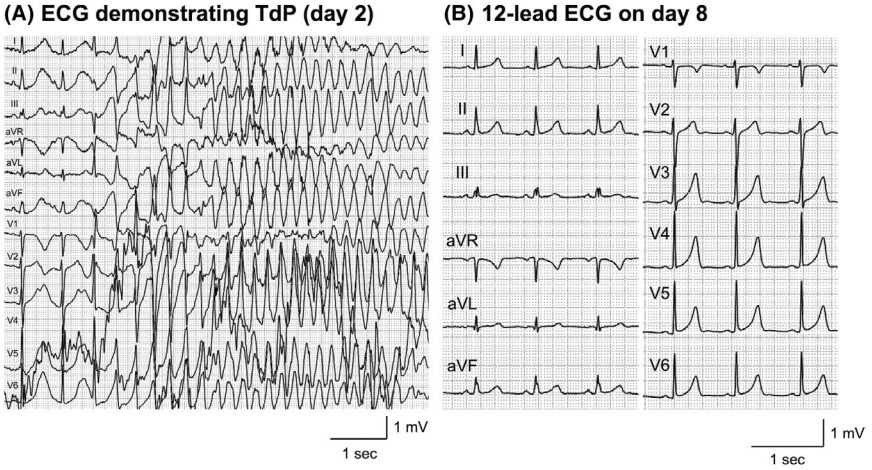

FIGURE 2 Twelve-lead surface ECGs of the patient on day 2 and day 8. A, ECG demonstrating torsade de pointes (TdP) on day 2. B, ECG on day 8 after admission showing normalized QT interval. QTc = 439 ms

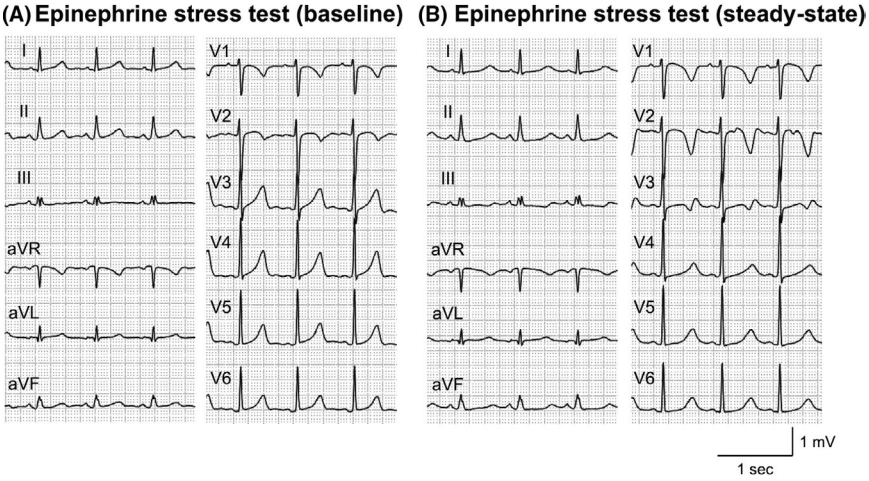

FIGURE 3 Twelve-lead ECGs at epinephrine stress test. A, Baseline (QTc = 491 ms). B, Steady-state (QTc = 683 ms)

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3 | DISCUSSION

We report a concealed type 1 LQTS case (*KCNQ1*-T587M) that was unmasked by the ingestion of *Pueraria mirifica*, a commercially available rejuvenating supplement, containing estrogen-like substances.[10,11] Estrogen was reported to prolong action potential duration and QT interval.[5-7] One of the proposed mechanisms is that 17β-estradiol (E2) can suppress I_{Kr} in a receptor-independent manner.[7] However, the suppression level was so small that its impact on baseline QTc interval was not prominent in the presence of repolarization reserve.[12] In fact, to the best of our knowledge, there are no reports of *Pueraria mirifica*-induced ventricular arrhythmias, and it is unlikely to cause dramatic changes in ECGs in healthy individuals.

Meanwhile, its estrogenic activity played a critical role in our patient by unveiling the most malignant phenotype of *KCNQ1*-T587M mutation, leading to refractory and repetitive TdP. The mutation was first reported to cause trafficking defects of $K_V7.1$ encoded by *KCNQ1*.[2] Later, it has been shown that the *KCNQ1*-T587M failed to function as a chaperone that transports hERG proteins (responsible for I_{Kr}) to the plasma membranes.[13,14] These multiple mechanisms that modulate both I_{Kr} and I_{Ks} may underlie malignant phenotypes which were often seen in the *KCNQ1*-T587M carriers. Therefore, estrogenic substances predisposed the patient to life-threatening arrhythmias by the decrease of repolarization reserve caused by *KCNQ1*-T587M.

4 | CONCLUSION

We report the first case of severe phenotype of type 1 LQTS unveiled by *Pueraria mirifica*.

CONFLICT OF INTEREST

The authors declare no conflict of interests for this article.

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