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**CASE REPORT**
*Arrhythmias/electrophysiology*

# PARP inhibitor-induced torsades de pointes in long QT syndrome: a case report

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**Background** Poly ADP-ribose polymerase (PARP) inhibitors target pathogenic *BRCA* mutations in chemotherapy-resistant malignancies. PARP inhibitors cause modest dose-dependent QT prolongation in the setting of a normal baseline QT interval.

**Case summary** We describe a case of PARP inhibitor-induced torsades de pointes (TdP) in an 86-year-old gentleman prescribed rucaparib due to chemotherapy-resistant, metastatic prostate cancer with pre-existing long QT, with an apparent dose-dependent increase in QT interval. The patient presented with syncope and recurrent TdP requiring direct cardioversion reversion (200 J biphasic) and an isoprenaline infusion (2 µg/min). There were no other QT prolonging agents and no electrolyte or metabolic disturbance to account for this arrhythmia. Improvement in QT interval was observed within 72 h of rucaparib cessation.

**Discussion** PARP inhibitors cause a modest, dose-dependent increase in QT interval in patients with a normal baseline. The safety of PARP inhibitors in patients with pre-existing long QT has not been evaluated. This is the first reported case of rucaparib-associated TdP in a patient with pre-existing long QT, highlighting the amplified effect of this agent in individuals with pre-existing QT prolongation and the risk of fatal arrhythmias.

**Keywords** Torsades de pointes • Long QT syndrome (LQTS) • Cardiotoxicity • hERG channel • PARP inhibitor • Case report

## Learning points

- Newer anticancer experimental therapies improve survival in patients with metastatic malignancies refractory to conventional treatments at the cost of increasing acute and chronic cardiotoxicity.
- Poly ADP-ribose polymerase inhibitors exhibit a dose-dependent modest increase in QT interval in patients with normal baseline QT and are likely to have an augmented effect in those with pre-existing QT prolongation, with an increased risk for fatal arrhythmias.

## Introduction

Recent advances in cancer therapy have improved the prognosis in many malignancies, though in some cases, at the cost of increased acute and chronic cardiotoxicity.[1,2]

Poly ADP-ribose polymerase (PARP) inhibitors target oncogenic mechanisms by inducing synthetic lethality in homologous recombination-deficient tumours.[3] The efficacy and safety of these agents are under evaluation in Phase I and II clinical trials.[4,5]

PARP inhibitors cause modest dose-dependent QT prolongation in the setting of a normal baseline QT interval.[6] We describe a case of PARP inhibitor-induced torsades de pointes (TdP) in a patient with

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castrate-resistant metastatic prostate cancer with pre-existing prolonged QT, highlighting the amplified effect of this drug in individuals with pre-existing QT prolongation.

## Timeline

| Time | Events |
|---|---|
| 2013 | Electrocardiogram (ECG) demonstrating first degree atrioventricular (AV) block with mild baseline QT prolongation (QTc 465 ms) |
| June 2018 | Rucaparib initiation for chemotherapy-resistant metastatic prostate cancer |
| October 2018 | ECG 3 months following initiation of rucaparib therapy demonstrating marked QT prolongation (QTc 589 ms) with no reported syncope |
| March 2019 | Hospital admission following syncope with development of torsades de pointes (TdP) requiring direct cardioversion (DC) shock to sinus rhythm |
| | ECG post-DC shock demonstrated markedly prolonged QT interval (QTc 680 ms), first degree AV block, and left bundle branch block |
| Day 1 | Recurrent TdP requiring DC shocks and initiation of isoprenaline infusion (rucaparib ceased) |
| Day 3 | Isoprenaline withdrawal with marked improvement in QT interval (QTc 547 ms) |
| Day 9 | Clinical deteriorated in the context of advanced metastatic prostate cancer despite rhythm stabilization. Palliated in accordance with patient's wishes |
| | Family members offered referral for genetic testing for possible inherited long QT |

## Case presentation

An 86-year-old man presented with syncope on a background of castration resistant metastatic prostate cancer. He had no pre-existing diagnosis of cardiovascular disease and no known intracranial or intracardiac metastases. He was enrolled in the TRITON-2 trial (NCT02952534; PR CO-338-052),[3] receiving oral rucaparib 600 mg twice daily for 9 months prior to the index admission. His only other regular medication was paracetamol.

Baseline and serial electrocardiogram (ECG) monitoring was not undertaken during the trial period and pre-existing prolonged QT on an earlier ECG from 2013 (QTc 465 ms) did not preclude him from enrolment in this trial. Left ventricular systolic function was preserved on transthoracic echocardiogram prior to enrolment. Following rucaparib initiation, he had no cardiac symptoms or hospital presentations until the index admission.

He presented with a collapse at home without a clear cause and no acute injuries. In the emergency department, he remained in sinus rhythm and was transferred to the ward on cardiac monitoring. Shortly after arriving on the ward, he developed TdP (*Figure 1*) with altered conscious status requiring brief cardiopulmonary resuscitation (30 s) followed by a single direct cardioversion shock (200 J biphasic) and 20 mmol/L intravenous magnesium sulphate. Post-arrest, he appeared pale and cachectic with no jaundice, murmurs, or signs of fluid overload. He had a Glascow Coma Scale of 15, with no signs of asterixis. ECG showed a broad junctional rhythm at a rate of 52 b.p.m. (left bundle branch block pattern) with marked U waves in V2–V4 and severe QT prolongation (QTc 680 ms) (*Figure 2*). Rucaparib was discontinued immediately. An ECG performed 5 years prior to rucaparib initiation demonstrated first degree atrioventricular block and a long QT interval (QTc 465 ms) (*Figure 3*). There was no personal history of coronary artery disease or syncope and no family history of cardiogenic syncope or sudden cardiac death.

Notably, an ECG performed 3 months following rucaparib initiation showed marked QT prolongation (QTc interval 589 ms, *Figure 4*), in the absence of syncope. Rucaparib continued as QT interval, both pre- and post-enrolment, are not routinely monitored as part of the TRITON-2 trial and the marked increase in QT interval was not documented during the trial follow-up. The patient did not undergo ECG or Holter monitoring following rucaparib initiation.

No other QT prolonging agents were prescribed. The only other regular medication was paracetamol 1 g up to four times per day for pain management in the setting of bony metastases. There was no electrolyte abnormality detected [serum potassium 4.4 mmol/L (normal range 3.5–5.0 mmol/L) and serum magnesium 1.0 mmol/L (normal range 0.7–1.1 mmol/L)] and both renal and hepatic function were satisfactory. Isoprenaline infusion (2 μg/min) was introduced due to recurrent rate-related TdP in the context of bradycardia.

On day 3 of admission, isoprenaline was ceased and the QT interval was notably shorter (QTc interval 547 ms; *Figure 5*) with an intrinsic heart rate of 93 b.p.m. in atrial flutter. Consideration was given to permanent pacing given an initial projected life expectancy of >12 months, however, despite rhythm stabilization, he deteriorated precipitously while in hospital, likely as a consequence of oncological disease progression with refractory symptoms in addition to the physiological insult of resuscitation in an elderly, already frail, cachectic gentleman with limited reserve. The patient was palliated, and the family subsequently declined post-mortem genetic testing or familial screening for inheritable long QT syndrome (LQTS).

## Discussion

Individuals with a normal baseline QT interval may experience up to 14 ms increase in QT interval with PARP inhibitor therapy;[6] however, individuals with pre-existing QT prolongation are at greater risk of a magnified effect and clinically relevant arrhythmia. Each 10 ms increase in QTc correlates to an approximate 5–7% increase in TdP risk.[7]

Though congenital LQTS may arise from mutations in multiple genes, almost all cases of drug-induced LQTS result from block of the human ether-a-go-go-related gene (hERG) channel (encoded by *KCNH2*).[8] The hERG potassium channel physiologically co-ordinates cell membrane repolarization. Inhibitors, such as rucaparib, bind to the hERG channels and inhibit repolarization, resulting in QT

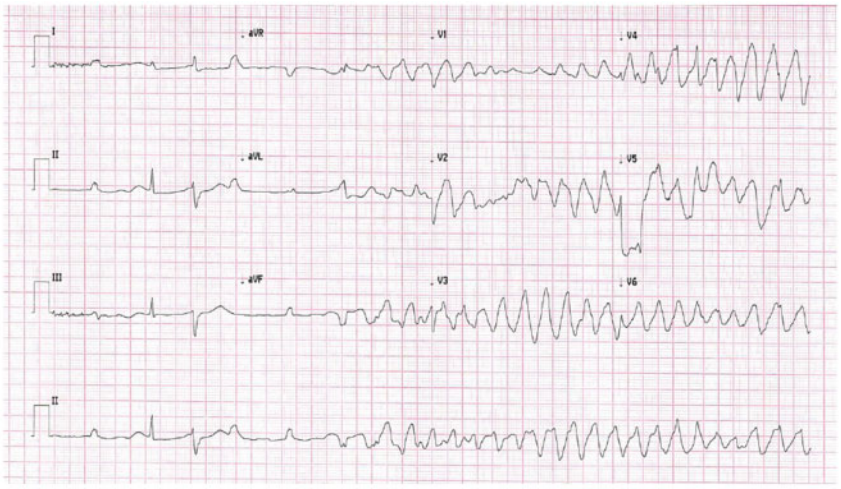

**Figure 1** Electrocardiogram demonstrating torsades de pointes.

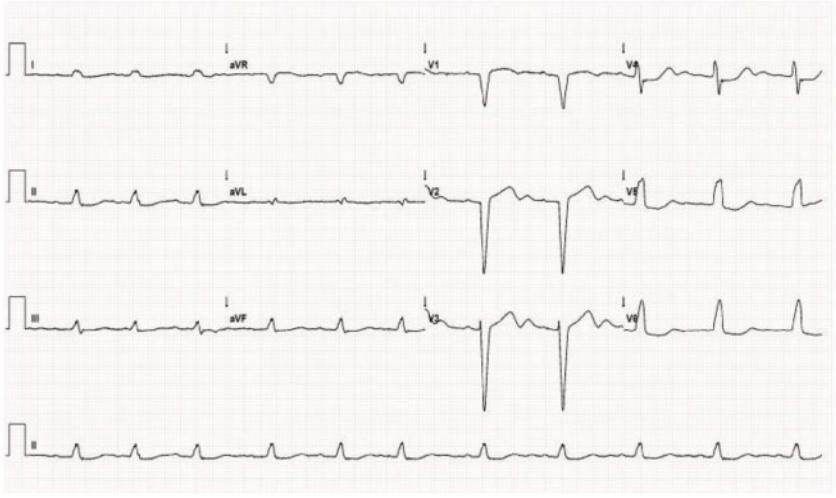

**Figure 2** Post-arrest electrocardiogram demonstrating markedly prolonged QT interval (QTc 680 ms).

prolongation in a dose-dependent manner.[6] The half maximal inhibitory concentration (IC50) of rucaparib against the hERG channel (at 22.6 μM) is 13-fold higher than the peak serum concentration of the drug at the recommended dose of 600 mg twice daily, reflecting high potency of rucaparib against hERG channels resulting in repolarization delays.[8] This is the hypothesized mechanism by which PARP inhibitors may precipitate QT prolongation.

Previous studies have reported a marginal increase in QT interval in healthy individuals receiving PARP inhibitors[7] and clinical trials of PARP inhibitors have historically excluded patients with baseline QT prolongation.[9–12] This case demonstrates the amplified effect of PARP inhibitors in individuals where the repolarization current is already reduced, which is the implication of a baseline long QT interval.

The presence of pre-existing long QT accentuated by exposure to a QT prolonging agent raises the suspicion of LQTS with resulting so called 'second-hit' phenomenon.[11,12] This is further supported by the rhythm stabilization seen at 72 h, just under five half-lives of rucaparib (median half-life 17 h).[6]

Moreover, the absence of metabolic derangement or electrolyte disturbance, coupled with a temporal increase in QT interval with regular rucaparib and absence of other offending agents or apparent drug interactions raises the concern of rucaparib-induced TdP in a susceptible individual with likely LQTS. Interestingly, the TRITON-2

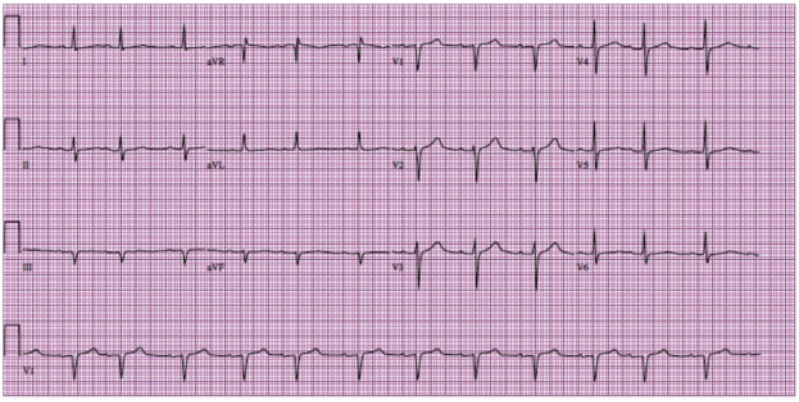

**Figure 3** Electrocardiogram in 2013 demonstrating first degree atrioventricular block (PR 223 ms) and prolonged QT interval (QTc 465 ms).

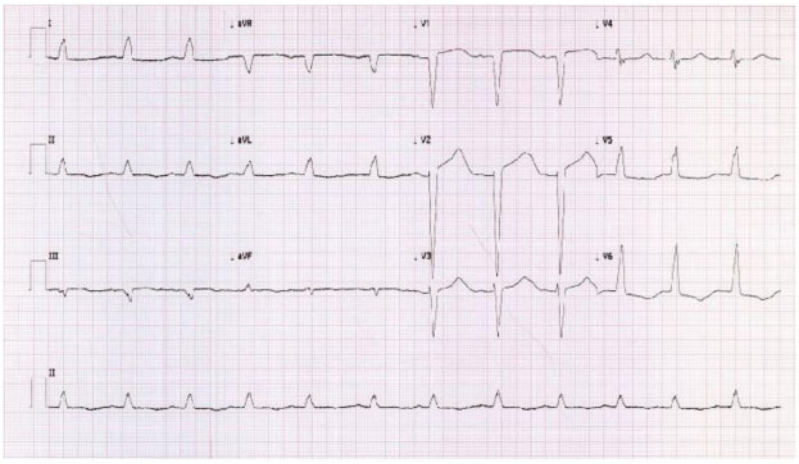

**Figure 4** Electrocardiogram 3 months after enrolment in TRITON-2 trial demonstrating left bundle branch block with prolonged PR and QT intervals (QTc 589 ms).

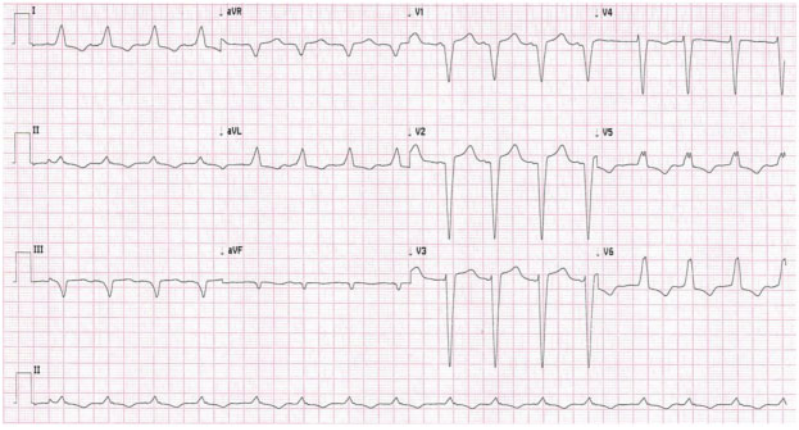

**Figure 5** Electrocardiogram following withdrawal of isoprenaline infusion demonstrating shorter QT interval (QTc 547 ms).

trial, unlike earlier studies of PARP inhibitors in metastatic malignancy refractory to standard therapies,[9–12] did not exclude patients with baseline QT prolongation.[3]

## Conclusion

This is the first reported case of rucaparib-related TdP in a patient with pre-existing long QT and emphasizes the importance of considering at-risk individuals at the time of pre-enrolment screening. Patients receiving PARP inhibitor therapies appear to exhibit a dose-dependent increase in QT interval, which is likely to be accentuated in individuals with pre-existing QT prolongation, amplifying the risk of cardiotoxicity and fatal arrhythmias.

Clinical trials of PARP inhibitors in chemotherapy-resistant metastatic malignancies have largely excluded patients with baseline QT prolongation, presumably due to the established dose–response relationship translating to a heightened risk of adverse cardiovascular sequelae.

This case reinforces the importance of judicious patient selection and appropriate interval monitoring in clinical trials of therapies with potential cardiotoxicity in the evolving era of cardio-oncology.

## Lead author biography

Dr Louise Segan is a Cardiology advanced trainee at Barwon Health. Her interests include device therapy and heart failure. She is a passionate advocate for gender diversity in Cardiology.

## Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

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