Abiraterone-induced refractory hypokalaemia and torsades de pointes in a patient with metastatic castration-resistant prostate carcinoma: a case report

Mariam Riad 1, Jeffery Scott Allison 2, Shahla Nayyal 3, and AbdulWahab Hritani 1,2*

1Internal Medicine Department, University of Alabama, Huntsville Regional Campus, Huntsville, AL 35801, USA; 2Cardiology Department, The Heart Center, Huntsville Hospital, Huntsville, AL 35801, USA; and 3Pharmacy Department, University of Colorado, Denver, Skaggs School of Pharmacy, Denver, CO 80045, USA

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Background
Abiraterone, an androgen deprivation therapy, has been used in the treatment of metastatic castration-resistant prostate cancer (mCRPC). It has been associated with increased risks of hypokalaemia and cardiac disorders. We report a case of torsades de pointes (TdP) associated with abiraterone use and refractory hypokalaemia in a man with mCRPC.

Case summary
A 78-year-old man with mCRPC presented to the emergency room for generalized weakness. Laboratory results revealed a potassium level of 2.2 mmol/L (3.5–5.0), magnesium level of 2.4 mg/dL (1.6–2.5), and normal kidney and hepatic functions. Initial electrocardiogram showed atrial fibrillation with rapid ventricular rate of 106 b.p.m., frequent premature ventricular contractions, and a QTc of 634 ms. The patient had multiple episodes of TdP, became pulseless and underwent advanced cardiac life support, including defibrillation. Despite a total of 220 mEq of intravenous potassium chloride, his potassium level only improved to 2.8 mmol/L. He received spironolactone and amiloride to promote urinary potassium reabsorption in addition to hydrocortisone, in an effort to reduce abiraterone’s effect on increasing mineralocorticoid synthesis.

Discussion
Abiraterone has been widely used in mCRPC since its approval by the Food and Drug Administration in 2011. Regulatory guidelines and standardized close QTc and electrolyte monitoring in patients may help prevent fatal arrhythmias associated with abiraterone.

Keywords
CYP17A1 inhibitor • Abiraterone • Prostate cancer • Hypokalaemia • Torsades de pointes • Case report

ESC Curriculum
5.6 Ventricular arrhythmia • 7.1 Haemodynamic instability • 7.3 Critically ill cardiac patient

*Corresponding author. Tel: +1 (256) 533-3388, Email: ahritani@theheartcenter.md
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Learning points

- Abiraterone should be used with caution in patients at high risk for developing ventricular arrhythmias.
- Regular standardized surveillance of QTc and electrolytes should be implemented for all patients on abiraterone and can potentially prevent the development of ventricular arrhythmias.
- Mineralocorticoid antagonist in addition to glucocorticoid therapy can be used to reverse the hypokalemic effect of abiraterone and should be considered for prevention as well.

Introduction

Cardiac arrhythmias have been reported with hormonal therapies for prostate and breast cancers through direct and indirect induction of arrhythmogenesis with and without electrolyte imbalances. The QT interval corrected for heart rate (QTc) is a measure of cardiac repolarization; if prolonged, it can be a harbinger of ventricular arrhythmias. Some androgen deprivation therapies are also associated with a possible risk of TdP. This effect can be potentiated by hypokalaemia caused by an excess in production of mineralocorticoids.

Abiraterone is a CYP17A1 inhibitor, FDA approved in 2011 for use in metastatic castration-resistant prostate cancer (mCRPC). Hypokalaemia has been associated with abiraterone use, for which concomitant use of low-dose prednisone has been recommended to reduce mineralocorticoid synthesis. There are no regulatory guidelines or monitoring for potential cardiac arrhythmias with the use of abiraterone. We report here a case of TdP with the use of abiraterone in the USA and review the relevant literature.

Timeline

| Day    | Event                                                                 |
|--------|----------------------------------------------------------------------|
| Day 1  | The patient presented with generalized weakness and severe hypokalaemia. He developed torsades de pointes (TdP) and was subsequently intubated for airway protection. |
| Day 2  | Hypokalaemia persisted and he was started on spironolactone, amiloride, and hydrocortisone. |
| Day 3  | Potassium level normalized. |
| Day 4  | Extubated successfully. |
| Day 5  | Transferred out of the CCU. |

Case presentation

A 78-year-old man with a history of hypertension and mCRPC on Abiraterone for 6 months presented to the emergency department (ED) with progressive generalized weakness and shortness of breath for 1 month, since his initial diagnosis of coronavirus disease-19 (COVID-19). He presented to his primary care office 3 weeks prior to his presentation to the ED with shortness of breath and tested positive for COVID-19 reverse transcription–polymerase chain reaction. He was managed in the outpatient setting with supportive symptomatic measures and self-quarantine. He had gradual improvement in his symptoms and repeat testing was negative for COVID-19 during this hospitalization. He was seen by his oncologist 2 months prior to his presentation to the ED and was found to have mild hypokalaemia on routine laboratory results for which he was prescribed oral potassium supplements. The patient’s home medications included losartan 50 mg, abiraterone 1 g, omeprazole 20 mg, potassium chloride (KCl) 10 mEq orally daily.

Physical examination was remarkable for a tachycardic rate and irregular rhythm consistent with atrial fibrillation. He had a normal S1 and S2 and no murmurs. Laboratory results revealed a potassium level of 2.2 mmol/L (3.5–5.0), magnesium level of 2.4 mg/dL (1.6–2.5), and normal renal and hepatic functions. Pro B-type natriuretic peptide was elevated at 3934 pg/mL and high-sensitivity troponin of 51 ng/L (upper limit of normal: 20). Initial electrocardiogram (ECG) (Figure 1) revealed atrial fibrillation with rapid ventricular rate of 106 b.p.m., frequent premature ventricular contractions, and a QTc of 634 ms.

Transthoracic echocardiogram (Video 1) demonstrated minimally reduced left ventricular ejection fraction of 45–50%. The right ventricle had normal cavity size and systolic function. Diastolic function could not be assessed due to the patient’s atrial fibrillation rhythm. He developed multiple episodes of TdP with loss of consciousness while in the ED (Figure 2) and he was subsequently intubated for airway protection.

The patient was admitted to the cardiac floor and he received a total of 160 mEq of intravenous KCl via peripheral intravenous access over 16 h, and 4 g of magnesium sulfate. Overnight, he developed recurrent episodes of TdP, which became more frequent and prolonged. He subsequently became pulseless and underwent advanced cardiac life support (ACLS), including defibrillation. He underwent one cycle of chest compressions and a single defibrillation with subsequent return of spontaneous circulation (ROSC), Post-ROSC vital signs: blood pressure 104/75 mmHg, heart rate 56 b.p.m., temperature 36.6°C, and respiratory rate 18 br/min and ECG was significant for bradycardia with a QTc of 670 ms (Figure 3). He was started on an intravenous lidocaine infusion in addition to a dopamine infusion to augment his heart rate and assist in shortening the QTc.

Despite a total of 220 mEq of intravenous KCl over 24 h, his potassium level only improved to 2.8 mmol/L. On the second day of his hospitalization, nephrology was consulted to assist in further management of his refractory hypokalaemia. He was started on

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Figure 1

Figure 2

Figure 3

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spironolactone and amiloride to promote urinary potassium re-absorption in addition to hydrocortisone, in an effort to reduce abiraterone’s effect on increasing mineralocorticoid synthesis.

His potassium level normalized on the third day of his hospital admission, was extubated on the fourth day, and was transferred out of the cardiac care unit on the 5th day without any further arrhythmias or QTc prolongation (Figure 4). His hospital stay was complicated by an aspiration pneumonia, from which he eventually recovered. He was discharged to a skilled nursing facility for subacute rehabilitation. The patient was instructed to discontinue abiraterone indefinitely and follow-up with his oncologist regarding further evaluation and management of his cancer. He was also started on dabigatran for full anticoagulation given his presentation with atrial fibrillation and high risk for stroke with CHA2DS2-VASc score of 3. He was instructed to follow-up with cardiology clinic. The patient was contacted by telephone for follow-up 3 months after discharge. He was symptomatically doing well, had normal electrolyte levels off of abiraterone, and was in the process of establishing care with a cardiologist in his hometown.

Discussion

Herein, we report a case of severe refractory TdP in a patient with a structurally normal heart, not on QT prolonging medication and while taking Abiraterone. Abiraterone in combination with prednisone has been widely used since its approval by the FDA in 2011 for patients with mCRPC, who had received prior chemotherapy. In 2012, it has been approved for use in all mCRPC and in 2018, it was approved for use in metastatic high-risk castration sensitive prostate cancer as well. Abiraterone has been shown to be associated with hypokalaemia and TdP.

TdP, French for ‘twisting of the points’ was first described by Dr Dessertenne in 1966 as a type of polymorphic ventricular tachycardia. The site of origin in TdP can occur in either ventricle, with the most common origin being the outflow tract areas. Prolonged QTc is an independent risk factor for TdP. A QTc >500 ms was found to be associated with increased risk of cardiac events and sudden death.8 Drug-induced QTc prolongation occur with numerous medications, many of which are listed on the CredibleMeds website.3 There are currently 65 medications associated with a known risk and 137 medications associated with a possible risk of TdP. Abiraterone is listed with a conditional risk of TdP with concomitant use of other QTc prolonging drugs, excessive dose, or with hypokalaemia.

Khan and Kneale9 reported a case of TdP associated with hypokalaemia and prolonged QTc in a patient with a known history of ischaemic heart disease and mCRPC on Abiraterone and prednisone. Rodieux et al.10 reported a patient with mCRPC on abiraterone and prednisone and no prior cardiac history who presented as a cardiac...
In 2010, a science advisory from the American Heart Association, American Cancer Society, and American Urological Association concluded that Androgen deprivation therapy (ADT) is associated with increased cardiovascular events.\textsuperscript{4} Furthermore, a case of transient systolic cardiac dysfunction that was reversed upon cessation of abiraterone has been reported.\textsuperscript{11} Bretagne \textit{et al.}\textsuperscript{6} analysed the cardiac effect of abiraterone vs. other ADTs, and they found an association with an increased risk of atrial arrhythmias, hypertension, congestive heart failure, and oedema. These cardiac events were more likely in patients with a history of hypertension and heart failure.

The cardiovascular adverse events with abiraterone can potentially be explained by the hypermineralocorticoid effect of abiraterone. Several randomized double-blinded placebo-controlled phase 3 trials that analysed the efficacy of abiraterone in patients with mCRPC demonstrated that hypokalaemia and cardiac disorders, most
commonly atrial tachycardias, were more common in the treatment group. Abiraterone is an CYP17A1 inhibitor, an enzyme with 17α-hydroxylase activity obligatory for androgen and cortisol synthesis. Blockade of this enzyme leads to inhibition of androgen and cortisol synthesis, while maintaining an uninhibited pathway for mineralocorticoid production. This decrease in glucocorticoid production reduces negative feedback on adrenocorticotropic hormone (ACTH). Under normal circumstances, ACTH does not significantly stimulate mineralocorticoid synthesis. However, when 17α-hydroxylase is inhibited, there is an increase in the production of corticosteroid precursors which are shunted towards the uninhibited mineralocorticoid synthesis pathway, leading to an increase in mineralocorticoid production. This leads to hypokalemia, fluid retention and oedema. Concomitant use of glucocorticoids has been shown to alleviate some of these adverse events by increasing negative feedback on ACTH and thus eliminating the hypermineralocorticoid state produced by abiraterone. However, the addition of corticosteroids may not be sufficient. Clinical trials analysed the use of abiraterone plus prednisone vs. placebo plus prednisone, and found more frequent atrial tachycardias, cardiac events and hypokalemia in the former group.

Our patient had been undergoing treatment with abiraterone for mCRPC for six months prior to his presentation. He had atrial fibrillation with a prolonged QTc and developed multiple refractory episodes of TdP, which deteriorated to ventricular fibrillation. His hypokalemia was refractory to treatment with large doses of intravenous KCl. His hypokalemia improved with the use of spironolactone, amiloride, and hydrocortisone. After removal of the offending agent, correcting hypokalemia, administering IV magnesium and increasing heart rate, IV lidocaine was used due to continued salvos of TdP. It is unclear what role, if any, his COVID-19 infection had in the development of TdP.

Further research is required to identify the risk factors for TdP in patients on abiraterone and to understand the mechanism of abiraterone-induced TdP, whether it is entirely related to the associated hypokalemia, the dose-related influence on QTc, if any. Regulatory guidelines and standardization of close QTc and electrolyte monitoring may help prevent fatal arrhythmias associated with abiraterone use.

Lead author biography

Mariam Riad, MD is originally from Egypt. She graduated medical school from Spartan Health Sciences University, St. Lucia. She is currently a third-year chief resident at the University of Alabama, Huntsville Internal Medicine Residency programme. She is interested in pursuing a Cardiology fellowship after residency.

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 authors confirm that written consent for submission and publication of this case report including images and associated text has been obtained from the patient in line with COPE guidance.

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