Syncope secondary to recurrent episodes of torsade de pointes following androgen-deprivation therapy: a case report

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ABSTRACT

Background : Abiraterone has applications in the treatment of prostate cancer. It can potentially be associated with various cardiac arrhythmias, such as torsade de pointes. We report a case where the patient experienced syncope episodes following the administration of this medication, and torsade de pointes was detected during monitoring.

Case summary: A 73-year-old man with a history of hypertension and prostate cancer presented to the emergency department with complaints of syncope. He was taking medications for his conditions, including abiraterone acetate and bicalutamide. An ECG revealed a prolonged QT interval and continuous cardiac monitoring showed multiple premature ventricular contractions (PVCs) followed by torsade de pointes. The

patient was admitted to the cardiac care unit, hypomagnesemia was corrected and abiraterone was discontinued.

Discussion: Abiraterone is a medication used to treat metastatic castration-resistant prostate cancer by inhibiting the enzyme CYP17A1, reducing androgen levels. However, it has been associated with cardiovascular toxicity, including an increased risk of cardiovascular events. Abiraterone can also prolong the QT interval, potentially leading to life-threatening arrhythmias. Additionally, it can cause hypokalemia and fluid retention due to redirection of corticosteroid precursors. The mechanism of hypogonadism in long QT syndrome is not fully understood, but there is evidence suggesting a link between testosterone deficiency and genetic abnormalities causing LQTS. Further research is needed to understand these relationships and identify appropriate treatment strategies. Regular monitoring for electrolyte disturbances and EKG status is recommended for patients taking abiraterone.

KEYWORDS

long QT, abiraterone acetate, bicalutamide, torsade de pointes, cancer therapy

INTRODUCTION

In adults, a typical QTc duration is more significant than 350 and less than 450 milliseconds for men and greater than 360 and less than 460 milliseconds for women (1). For every additional ten milliseconds, the probability of having arrhythmic events increases by around 5%. The reasons behind QT prolongation can be categorized into two groups: congenital or acquired (2). The hereditary condition known as long QT syndrome (LQTS) is caused by genetic abnormalities that impact particular regulatory proteins or ion-channel subunits. It may manifest in a variety of ways (3). LQTS alters the electrical activity of the heart and increases the risk of severe irregular heart arrhythmias that can potentially be fatal. This syndrome is characterized by a prolonged QT interval detected on the electrocardiogram (ECG). It can develop consequences including loss of consciousness, syncope, as well as ultimately fatal sudden cardiac death (SCD) (4).

Medication-induced LQTS is a frequently detected etiology of acquired LQTS, and a diverse spectrum of drugs triggers it. Comprehending the mechanisms that promote drug-induced LQTS is fundamental for identifying and preventing heart arrhythmias in patients who are prescribed these drugs. Several medications can inhibit the potassium channels that are essential for the process of cardiac repolarization. The result can lead to an elevated likelihood of experiencing heart arrhythmias and prolong the QT interval.

Medications such as antiarrhythmics, antibiotics, antipsychotics, antihistamines, and antidepressants are commonly associated with LQTS. Close monitoring of patients on these medications is necessary to detect any arrhythmias and symptoms associated with QT prolongation (5,6). The acquired form of QT prolongation is more frequent than the congenital form. It is usually caused by structural heart conditions (such as myocardial infarction, heart failure, and left ventricular hypertrophy) and also by drugs that prolong the QT interval (7).

Despite this, an extended QT interval can indicate possible causes for arrhythmias, including an increased incidence of PVCs and Torsade de pointes (TdP) (8,9). TdP is a type of ventricular tachycardia usually associated with LQTS. QRS complex is identified by the twisting around the isoelectric line on the ECG and possesses a risk of deteriorating into ventricular fibrillation, which can result in death (10). The prolonging of the QT interval caused by particular medications is commonly acknowledged as raising the probability of drug-induced TdP. The potential of developing TdP is related to the severity of QT prolongation. Indicators such as being female, having abnormal levels of electrolytes, and bearing a genetic tendency to LQTS are considered risk factors for TdP (11).

Pharmacological treatment utilizing beta-blockers, potassium channel blockers, or sodium channel blockers can also be applied to control arrhythmias and prevent recurrence. The choice of using medication for drug-induced LQTS or TdP should be cautiously addressed in each instance, taking into account the potential advantages concerning the dangers of triggering proarrhythmic consequences (12).

Case History/examination

A 73-year-old male with previous diagnoses of hypertension and prostate cancer was diagnosed three months ago, and the patient's treatment started eight weeks ago; he was taken to the emergency department because of an ongoing complaint of dizziness episodes and snoring with convulsive movement, notably as sleeping, since two weeks ago. He experienced two syncope episodes in the last week but did not have any prodromes such as palpitations, blurred vision, lightheadedness, feeling hot, nausea, or sweating. His companions mentioned that he did not develop urinary incontinence, tongue biting, or paleness after the syncope episodes. Syncope episodes occurred while sitting, lasting 10 to 20 minutes, and the patient snored. He had not had a coronary evaluation and did not indicate any family history of heart disease and SCD.

The vital signs were a body temperature of 37.5, BP of 130/85 mm Hg, pulse rate of 70 beats/min, respiratory rate of 12 breaths/min, and oxygen saturation of 96% without supplemental oxygen during the initial examination. Auscultation of the heart in the emergency room showed a regular heartbeat. Electrocardiogram (ECG): sinus rhythm and QTc interval 625 ms (Fig. 1). We noticed a prolonged QT interval in his ECG. (Calculated with Bazett's formula)

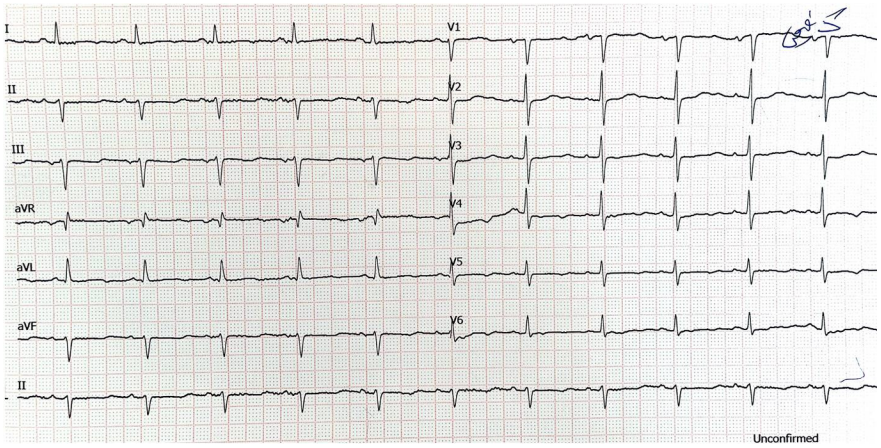
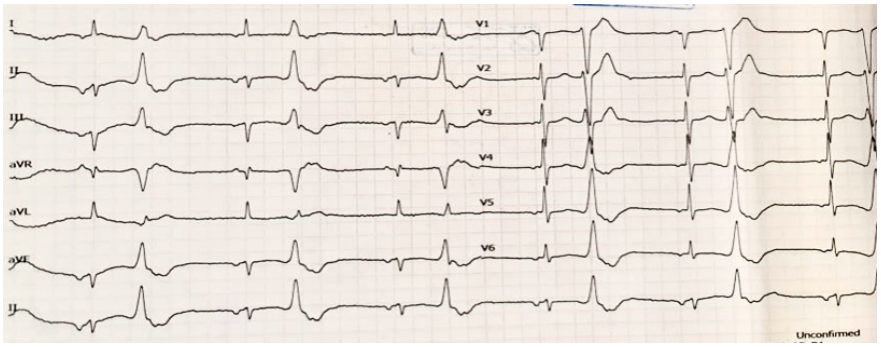


Figure 1

Methods:



We admitted the patient to the coronary care unit (CCU) to determine the cause of his syncope episodes and for further investigations. While in the CCU, he was placed under continuous cardiac monitoring. Multiple premature ventricular contractions (PVCs) were observed during monitoring, followed by torsade de pointes. (Figure 2, Figure 3)

Figure 2

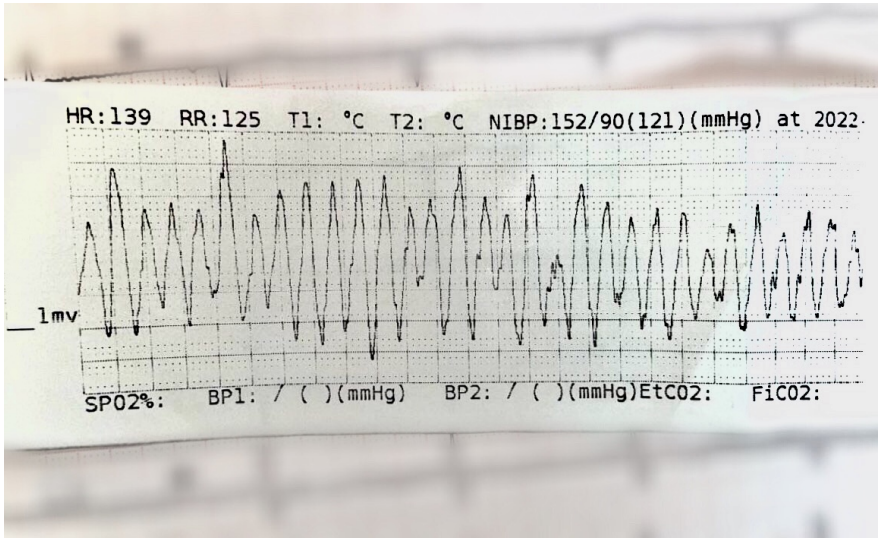


Figure 3

We promptly delivered a synchronized biphasic shock of 150 joules, restoring the abnormal rhythm (figure 4).

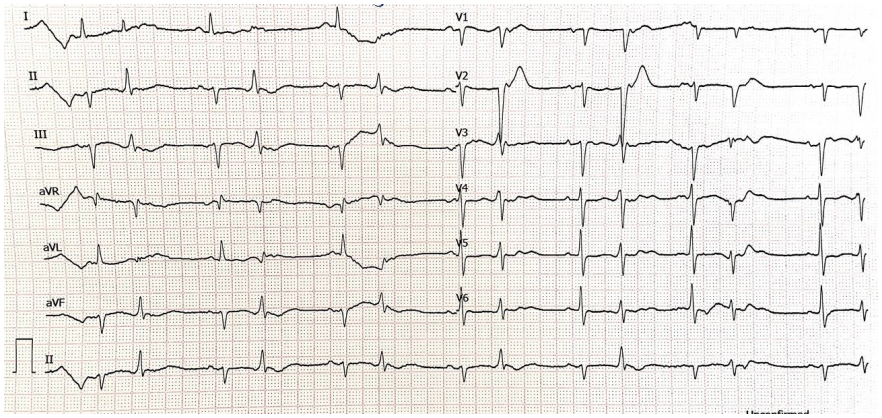


Figure 4

We temporarily held abiraterone acetate and bicalutamide use because they can cause prolonged QT intervals. The answer to the patient's initial tests was prepared during this period. The results were as follows*: hemoglobin 14.8 g/dL, glomerular filtration rate (GFR) 73.2 mL/min/1.73 m2, creatinine (Cr) 1 mg/dL, potassium 3.8 mmol/mL, magnesium 1.7 mg/dL,* ***calcium 9.5 mg/dL,*** **serum albumin** ***3.5 g/dL, troponin 19.7 ng/mL, TSH 2 mIU/L (NL:0.5 to 5.0 mIU/L), AST 49 U/L, ALT 52 U/L, ALP 86 IU/L.*** the blood test showed that he had low magnesium levels. The low magnesium levels led to the development of PVC and torsade de pointes. We immediately started him on intravenous magnesium supplementation (MGSO4, 1 to 2 gr in 10 cc DW5% over 2 min and 1gr /hour infusion for 24 hr) to raise his magnesium levels and prevent further cardiac events. We also monitored his heart rhythm closely with continuous cardiac monitoring. Even though we treated the patient's hypomagnesemia, he still had a prolonged QT interval. The CT scan of the brain and lungs showed the expected results.

Conclusion and Results

we did not see any significant dysrhythmias during the ECG Holter monitoring. An oncology consultation was conducted to modify the anti-cancer medication, and then we monitored the patient for several days. After restoring the QT interval, the patient was discharged.

DISCUSSION

Abiraterone is an androgen synthesis inhibitor, and its use is to treat metastatic castration-resistant prostate cancer. The drug works by inhibiting the enzyme CYP17A1, which produces androgens such as testosterone. The medication lowers androgen levels, which can inhibit the growth of prostate cancer. While Abiraterone is generally well-tolerated, it has been associated with cardiovascular toxicity. One study found that treatment with Abiraterone has been related to a more significant risk of cardiovascular events, including hypertension, atrial fibrillation, and heart fai lure (13,14).

QT interval extending has been linked to Abiraterone, and this could increase the risk of potentially fatal arrhythmias such as TdP. *Bicalutamide* is a medication that is primarily used to treat prostate cancer. Although it is generally well-tolerated, bicalutamide can have some side effects, including cardiovascular effects. Abiraterone is this patient's primary cause of torsade, although bicalutamide has a synergistic effect by prolonging the QT interval. Abiraterone inhibits the CYP17A1 enzyme, which produces androgen and cortisol hormones. By blocking this enzyme, Abiraterone reduces the synthesis of these hormones while allowing the production of mineralocorticoids to continue. This results in a decrease in the production of glucocorticoids, which generally provide negative feedback on the hormone ACTH. When the enzyme is inhibited, corticosteroid precursors are redirected toward producing mineralocorticoids, increasing their levels. This increase causes hypokalemia (low potassium levels), fluid retention, and swelling in the body. The current collection of literature regarding the pathophysiological mechanisms of hypogonadism in LQTS is quite limited.

Nevertheless, specific research proposes that a potential outcome of the genetic defects responsible for LQTS could be a shortage in testosterone. The study found that males diagnosed with LQTS demonstrated reduced levels of testosterone compared to individuals without the condition. Additionally, there was an observed negative relationship between testosterone levels and the duration of the QT interval. According to the authors, the genetic anomalies responsible for LQTS may potentially impact the synthesis and control of testosterone, hence resulting in the development of hypogonadism. The administration of testosterone replacement treatment resulted in a notable decrease in the duration of the QT interval in males diagnosed with hypogonadism. This finding implies that insufficient levels of testosterone may play a role in the onset and advancement of LQTS. The hERG channel, a distinct type of ion channel, plays a critical role in maintaining regular cardiac activity (15).

In summary, while the exact mechanism of hypogonadism in long QT syndrome is not yet fully understood, there is evidence to suggest that testosterone deficiency may be a consequence of the genetic abnormalities that cause LQTS. Further research is needed to elucidate the relationship between LQTS and hypogonadism fully and to identify potential treatment strategies. In addition, it is necessary to carry out more studies on the risk factors of abiraterone arrhythmogenesis, and patients with a higher risk should be regularly checked for electrolyte disturbances and EKG status after taking workup.

Statement of CONSENT The patient's family has consented to the participation of this case report. The patient's next of kin (according to our hospital policy, the eldest male child) has consented to the publication of this case report.

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Acknowledgements

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Conflicts of interest No conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT The data that support the findings of this study are available from the corresponding author [AB], upon reasonable request.

ETHICAL APPROVAL In this study, no additional costs and procedures were imposed on the patient's family members. We reported the retrograde standard treatment process of the patient. We maintained the patient's privacy.

Key Clinical Message: Chemotherapy medications like abiraterone acetate may induce QT prolongation. Cancer patients experiencing appetite loss are vulnerable to electrolyte imbalances like hypokalemia and hypomagnesemia, enhancing the risk of fatal arrhythmias such as Torsade de Pointe.

Authorship List:

Ali Bozorgi :Supervision, Writing – original draft, Writing – review & editing

Houshang Bavandpour karvane:Writing – original draft

Hamidreza Karimi:Validation

Mahsa Nikkhoo:Writing – review & editing

REFERENCES:

Summary Figures

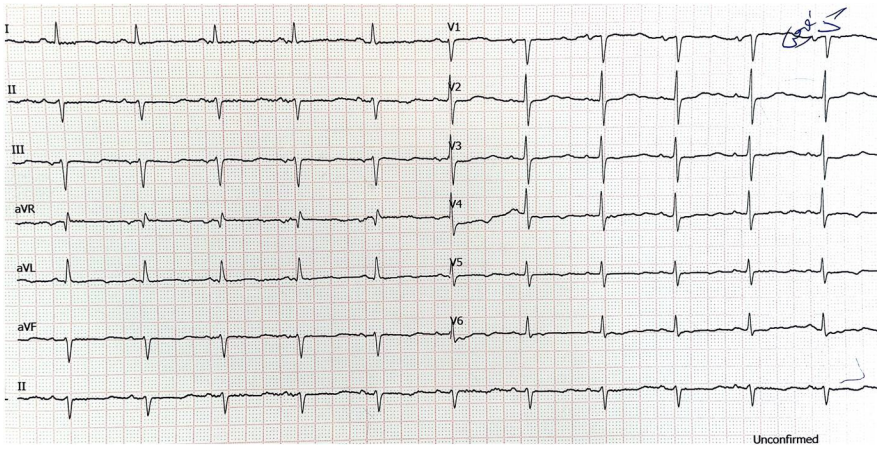

Figure 1

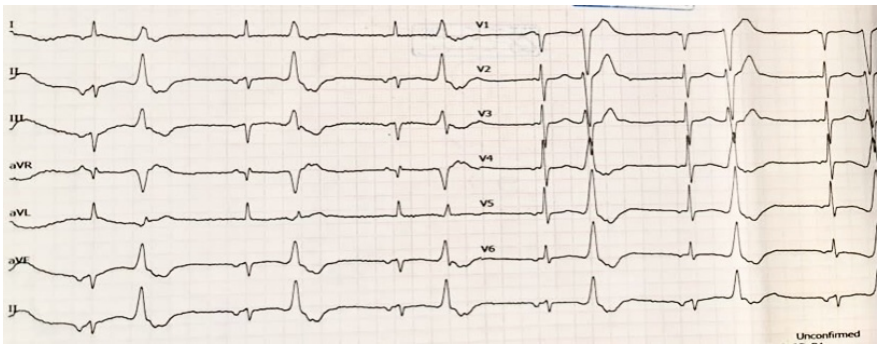

Figure 2

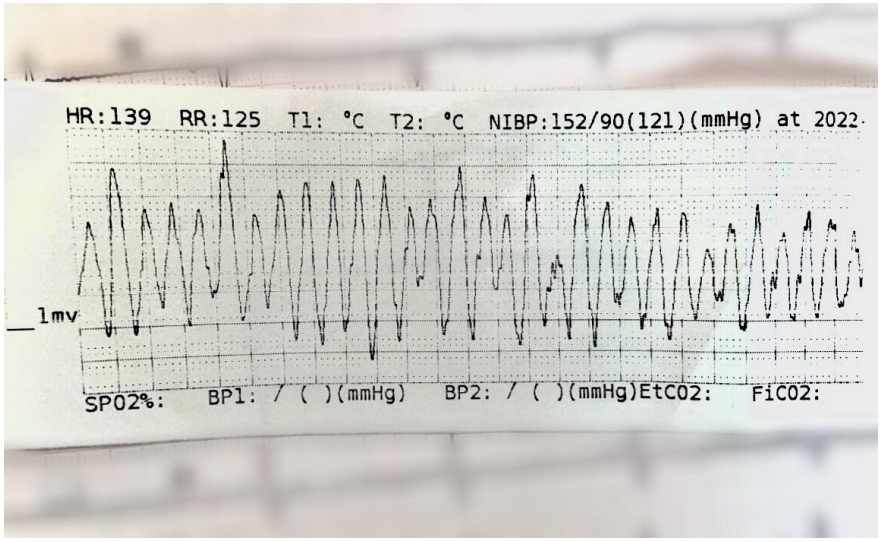

Figure 3

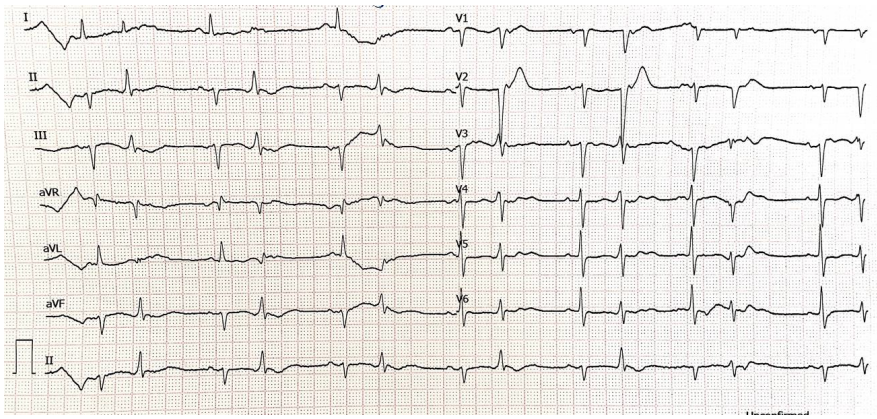

Figure 4

FIGURE LEGENDS:

Figure 1. Normal sinus rhythm, left axis deviation, left anterior hemiblock, long QTc: 625 ms (calculated with Bazett's formula)

Figure 2. Sinus rhythm with frequent premature ventricular complexes in a pattern of bigeminy

Figure 3. *Irregular rhythm,* Torsade de pointes

Figure 4. Aftershock EKG; Sinus rhythm with frequent premature ventricular complexes in a pattern of bigeminy, prolonged QT (QTc 708ms)

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therapy-a-case-report