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Case Report

A Rare Case of Severe Hypokalemia and Hypomagnesemia due to Venetoclax and Polypharmacy Leading to Life-Threatening Cardiac Arrhythmias

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Venetoclax · Hypokalemia · Arrhythmia · Torsades

Abstract
Venetoclax is a novel agent used in hematologic malignancies. Although no long-term studies have directly implicated venetoclax, few studies show possible association with electrolyte abnormalities. Severe derangements in serum electrolyte levels can cause cardiac dysrhythmias, which can be potentially fatal. We present a case of venetoclax in association with the other medications causing life-threatening arrhythmias. Hypothesized mechanisms include damage to the distal tubules causing loss of potassium and magnesium. Our patient required modification of his medications and aggressive repletion of electrolytes with good outcomes. For patients on venetoclax, especially those with polypharmacy, caution should be exercised to prevent severe electrolyte derangements, which can lead to life-threatening arrhythmias.

Introduction

Venetoclax is a novel chemotherapy agent which is a BH3-mimetic BCL-2 inhibitor leading to apoptosis of leukemia cells. It is utilized for the treatment of acute myeloid leukemia (AML) and chronic lymphoblastic leukemia [1]. Few studies have reported a possible association of electrolytes disturbance during treatment with venetoclax, as this was mainly attributed to tumor lysis syndrome that can lead to cardiac arrhythmias and acute

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kidney injury [2, 3]. Studies have shown that low extracellular potassium levels paradoxically reduce rapid potassium current (IKr) by enhanced inactivation or exaggerated competitive block by sodium, thus leading to QT interval prolongation and possible torsades de pointe [4]. We report a case with AML on venetoclax with ciprofloxacin and posaconazole for chemoprophylaxis, producing severe hypokalemia and hypomagnesemia, leading to QT prolongation and subsequent torsades de pointes, with improvement after adjustment of these medications. We intend to provide additional information and raise awareness regarding the possible adverse effects of venetoclax when combined with other medications leading to severe electrolyte disturbance and life-threatening arrhythmias to aid clinicians in better utilization of this drug. Furthermore, this case report opens additional venues for studies regarding the potential side effects of venetoclax.

Case Presentation

An 81-year-old male with a past medical history of paroxysmal atrial fibrillation, diastolic heart failure, hypertension, type 2 diabetes mellitus, chronic kidney disease (CKD), anemia of CKD, and acute myeloid leukemia on venetoclax and chemoprophylactic medications including ciprofloxacin 500 twice daily, posaconazole 300 once daily, amiodarone 200 mg daily, Toprol XL 50 mg daily, acyclovir 400 mg twice, venetoclax 400 mg daily was presented to the ED after a witnessed syncopal episode at home with no stigmata of seizure activity for 3 min. He was evaluated by his cardiologist the day prior to admission and was found to be hypotensive with worsening kidney function, leading to the discontinuation of benazepril, his long-term hypertensive medication. On arrival, the patient had heart rate of 34 and blood pressure of 159/69. Physical exam was remarkable for bradycardia, pale skin, bilateral +1 pitting edema, hepatomegaly, and splenomegaly. Laboratory evaluation was significant for hypokalemia with potassium (k+) of 2.8 mmol/L, magnesium (Mg^{2+}) of 1.5 mg/dL, acute kidney injury on CKD, with creatinine of 2.01, and blood urea nitrogen of 44 (baseline creatinine 1.25 and blood urea nitrogen 20), albumin 3.4 g/dL, and pancytopenia. There was no orthostatic drop in BP. EKG revealed normal sinus rhythm with U waves and prolonged QT interval >600 msec, as shown in Figure 1. Telemetry revealed two episodes of torsades de pointes, both initiated with sinus bradycardia, prolonged QT interval, PVCs, and long, short sequences likely due to hypokalemia induced by venetoclax and polypharmacy. Venetoclax was discontinued, and ciprofloxacin and posaconazole were changed for cefepime and isavuconazole, respectively. Amiodarone, metoprolol, and torsemide were discontinued indefinitely. K+ and Mg were aggressively replenished, with a progressive uptrend of electrolytes noted after stopping venetoclax, as shown in Table 1. Subsequent EKG showed improvement of the QT interval alongside a resolution of U waves and subsequently reverted to sinus bradycardia, as demonstrated in Figure 2. The patient was discharged home on augmentin and isavuconazole with close follow-up with a hematology-oncology and cardiology.

Discussion

We present a patient on venetoclax who developed significant hypokalemia and QT prolongation leading to syncope. This patient was on concomitant medications that worsened QT prolongation, such as amiodarone for atrial fibrillation, and prophylactic antimicrobials, such as ciprofloxacin and posaconazole. The hypokalemia improved on stopping venetoclax and switching the ciprofloxacin and posaconazole for less QT-altering medications like amoxicillin-clavulanate and isavuconazole. Venetoclax is a highly selective oral BH3-mimetic

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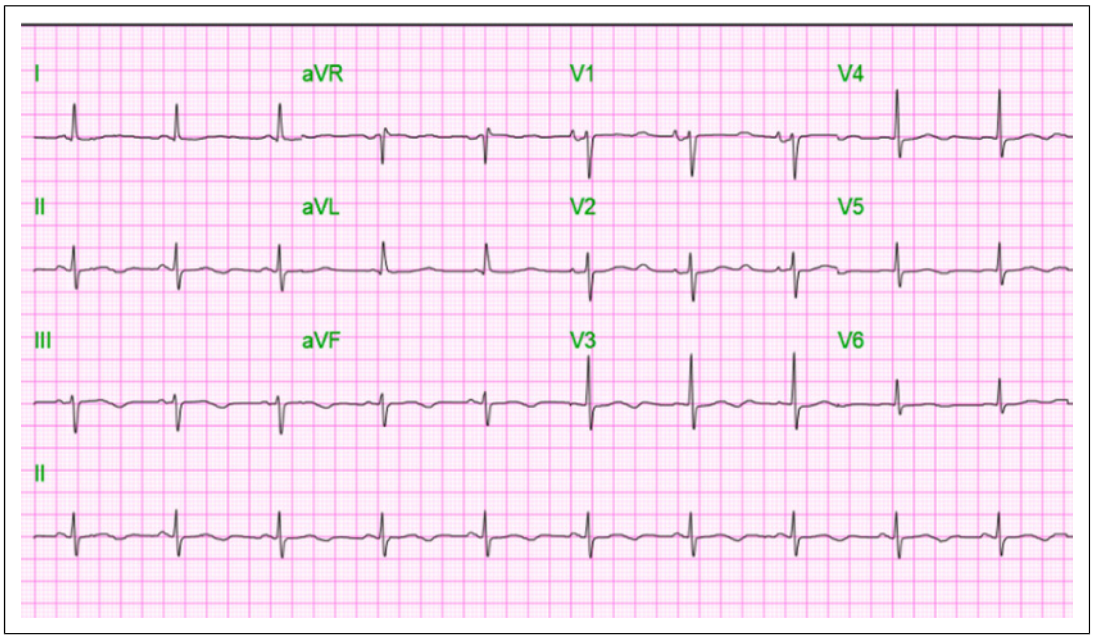

Fig. 1. 12-lead EKG on presentation demonstrating normal sinus rhythm with a heart rate of 60 beats per minute, U waves noted in V2 and V3, and prolonged QT interval >600 msec.

BCL-2 inhibitor leading to apoptosis of leukemia cells, approved for leukemia treatment and in multiple myeloma cells [1]. Few physicians are aware of the potential side effects of this new drug. Phase II trials of venetoclax for AML showed the occurrence of electrolyte abnormalities in 20–40% [2, 3]. Venetoclax may potentially lead to renal toxicity by causing damage to the proximal and distal tubules in the kidneys, resulting in the loss of potassium and magnesium, as hypothesized by Lubbe [3]. Only a few reported cases and studies have been published that show venetoclax causes electrolyte imbalances like hypokalemia and hypomagnesemia. Still, they were mainly found to be asymptomatic or attributed to antimicrobial prophylaxis medications or underlying cancer [2, 5]. The literature suggests measuring urinary electrolytes, but our patient did not have urinary electrolytes measured. Our patient developed potentially fatal symptoms like torsades. This could have been caused by an additive effect using multiple medications worsening QT prolongation with severe superimposed hypokalemia caused by venetoclax. Previous studies hypothesized that venetoclax does not cause significant QT prolongation [6, 7], although this was not a statistically significant result. We need more studies to support or reject this hypothesis. In this study, we intend to aid physicians to remain vigilant about electrolyte derangements as a possible complication caused by venetoclax, when combined with other medications with similar side effects to avoid life-threatening arrhythmias. Patients on multiple medications like chemoprophylactics like posaconazole (which has been shown to worsen toxicity with venetoclax) and antiarrhythmics, which could cause electrolyte imbalances and the complications from diseases like tumor lysis syndrome should not be overlooked [2, 5, 8]. Close monitoring of kidney functions and electrolytes is required when using venetoclax and avoiding medications that cause similar complications if possible. Measuring urine electrolytes is recommended if venetoclax toxicity is suspected. For our patient, we improved the hypokalemia by holding venetoclax, switching antibiotic prophylaxis ciprofloxacin to a cephalosporin, posaconazole with isavuconazole, and lowering the dose of the amiodarone, resulting in slow improvement in QT prolongation.

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Table 1. Serum levels of potassium and magnesium

	Hospital day 1	Hospital day 2	Hospital day 3	Hospital day 4
Potassium	2.8	4.4	4.2	4.5
Magnesium	1.5	1.8	2.2	1.9

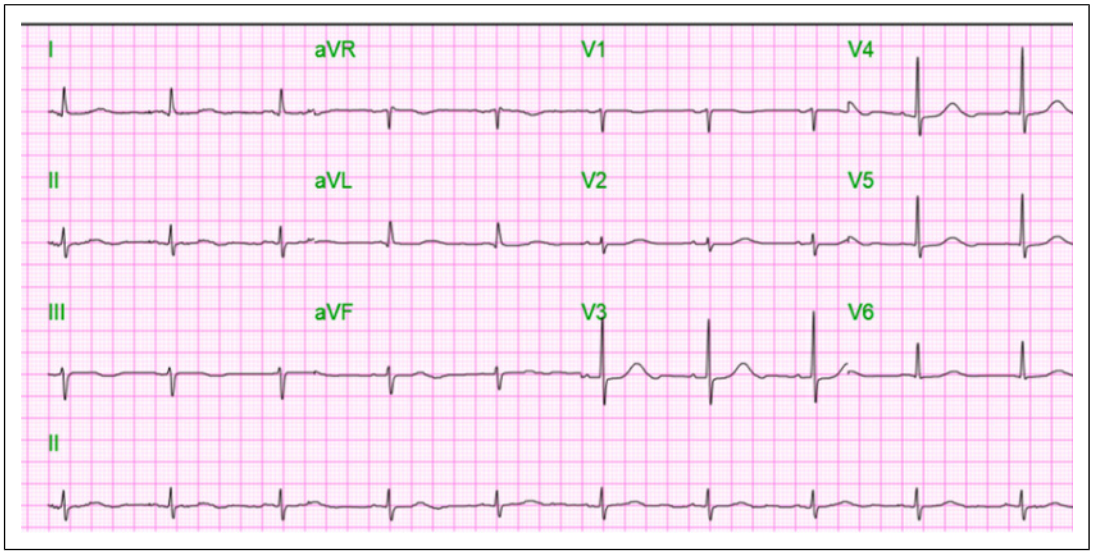

Fig. 2. 12-lead EKG on hospital day 4 demonstrating normal sinus rhythm with HR 60 beats per minute and prolonged QT interval at 560 msec.

Conclusion

As newer therapeutic agents are introduced for the treatment of malignancies, many providers are often unaware of the potential adverse events and drug-drug interactions. We recommend cautious concomitant use of other medications like chemoprophylactic and antibiotic prophylactics, plus vulnerable groups like CKD and arrhythmias, which can potentially cause hypokalemia and QT prolongation. The use of venetoclax in these patients would require closer monitoring of electrolytes and kidney function to avoid fatal adverse events. Our case presents such a situation where venetoclax, in conjunction with other medication could lead to an unfortunate and life-threatening event. However, additional studies are required to find a direct association between venetoclax and electrolyte abnormalities and establish its interaction with other drugs. The CARE Checklist has been completed by the authors for this case report, and is attached as supplementary material (for all online suppl. material, see https://doi.org/10.1159/000534135).

Statement of Ethics

The paper is exempt from Ethical Committee approval due to the nature of reporting based on daily clinical practice. This retrospective review of patient data did not require ethical approval in accordance with local/national guidelines. Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Laura Torres Cruz, Sai Priyanka Pulipaka, Neenu Anthony, and James Liu were involved in data collection and writing the manuscript. Maryam Barkhodarian, Ahmad Al Awwa, and Simcha Weissman were involved in editing and revising the manuscript.

Data Availability Statement

All data generated during this study are included in this article. Further inquiries can be directed to the corresponding authors.

References

1 Roberts AW. Therapeutic development and current uses of BCL-2 inhibition. Hematology Am Soc Hematol Educ Program. 2020 Dec 4;2020(1):1–9.
2 Davids MS, Roberts AW, Seymour JF, Pagel JM, Kahl BS, Wierda WG, et al. Phase I first-in-human study of venetoclax in patients with relapsed or refractory non-hodgkin lymphoma. J Clin Oncol. 2017 Mar 10;35(8):826–33.
3 Van der Lubbe N, Lugtenburg PJ, Hoorn EJ. Electrolyte disorders secondary to venetoclax. Clin Kidney J. 2020 Jun 15;14(4):1272–4.
4 Verzicco I, Regolisti G, Quaini F, Bocchi P, Brusasco I, Ferrari M, et al. Electrolyte disorders induced by antineoplastic drugs. Front Oncol. 2020 May 19;10:779.
5 Konopleva M, Pollyea D, Potluri J, Chyla B, Hogdal L, Busman T, et al. "Efficacy and biological correlates of response in a phase II study of venetoclax monotherapy in patients with acute myelogenous leukemia". Cancer Discov. 2016;6:1117–1106.
6 Kallergis EM, Goudis CA, Simantirakis EN, Kochiadakis GE, Vardas PE. Mechanisms, risk factors, and management of acquired long QT syndrome: a comprehensive review. Sci World J. 2012;2012:212178.
7 Freise KJ, Dunbar M, Jones AK, Hoffman D, Enschede SL, Wong S, et al. Venetoclax does not prolong the QT interval in patients with hematological malignancies: an exposure-response analysis. Cancer Chemother Pharmacol. 2016 Oct;78(4):847–53.
8 Agarwal SK, DiNardo CD, Potluri J, Dunbar M, Kantarjian HM, Humerickhouse RA, et al. Management of venetoclax-posaconazole interaction in acute myeloid leukemia patients: evaluation of dose adjustments. Clin Ther. 2017 Feb;39(2):359–67.