CASE REPORT

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# Deciphering the Role of Combination Therapy of Cobimetinib, Vemurafenib, and Antidepressant Drugs in QTc Prolongation and Torsade De Pointes (TDP) in Malignant Melanoma

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**ABSTRACT** Tyrosine kinase inhibitors (TKIs), particularly the combination of MEK inhibitors (cobimetinib and trametinib) and BRAF inhibitors (vemurafenib and dabrafenib), are now considered as the first-line treatment of patients with BRAF V600-mutated metastatic melanoma. Most cancer patients are on antidepressant drugs. In several case reports, vemurafenib has been reported for its adverse effects, such as nephrotoxic and cardiotoxic effects, including QTc prolongation. The antidepressant drugs, such as escitalopram and mirtazapine are also among the class of drugs that were reported to cause QTc prolongation and cardiac arrhythmias. This study is based on a patient with malignant melanoma and the investigation on combination therapy of vemurafenib, cobimetinib, and concomitant antidepressant drugs (escitalopram and mirtazapine). The patient had a history of recurrent syncope episodes, hypokalemia, QTc prolongation, and Torsades De Pointes (TDP). The drug therapy was discontinued, and intracardiac defibrillator (ICD) was implanted for patient's safety. Furthermore, QTc prolongation and hypokalemia were persistent after drug discontinuation, indicating some degree of renal and/or cardiac injury. The patient was discharged on beta-blocker and potassium replacement therapy.

**Keywords:** Antidepressant drugs; cardiotoxicity; cobimetinib; malign melanoma; nephrotoxicity, and vemurafenib

Tyrosine kinase inhibitors (TKIs), particularly the combination of MEK inhibitors (cobimetinib and trametinib), and BRAF inhibitors (vemurafenib and dabrafenib) is now considered as the first-line treatment of patients with BRAF V600-mutated metastatic melanoma. The common side-effects of BRAF inhibitors are cutaneous toxicity, nephrotoxicity, and cardiotoxicity.[1] In a previous clinical study, the combined administration of vemurafenib and cobimetinib has been associated with cardiotoxicity (heart failure) and QTc prolongation, that persisted after the discontinuation of therapy but returned to normal after six months. The patient was discharged with an implantable intracardiac defibrillator (ICD) for safety.[2] Most TKIs significantly increase the QT interval, while the incidence of arrhythmias was noted highest in vemurafenib.[3] Additionally, vemurafenib might induce severe acute renal failure, including persistent renal injury.[4] Though, the result from the previous clinical study which was based on 38 patients, showed that the adjunction of MEK inhibitor to vemurafenib in the treatment of metastatic melanoma reduces the incidence and severity of nephrotoxicity compared to monotherapy in a study of 38 patients, while a phase IB dose-escalation study of the cobimetinib and duligotuzumab showed that the 26% of the patients experienced hypokalemia, further indicating cobimetinib which might have some adverse effects on the renal tubular system.[5,6]

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The cardiovascular side-effects of antidepressants are well established. These drugs usually affect the cardiac action potential (AP), lengthening of both depolarization and repolarization phases, further leading to QRS widening, QT interval prolongation, or causing Brugada-like electrocardiogram patterns.[7]

The objective of this case report is to highlight how the concomitant use of antineoplastic drugs and antidepressants, in cancer patients, can have a synergistic effect with some lethal side-effects, such as hypokalemia, QTc prolongation, and Torsade De Pointes (TDP).

## CASE REPORT

A 68 years-old-female patient with malign melanoma was admitted in our emergency department with syncope of recurrent short-lasting episodes. The patient was conscious, and her physical examinations were normal. The electrography (ECG) taken in the emergency department, read QT as 700 ms with frequent ventricular extrasystole (Figure 1). Bedside echocardiography showed no structural heart disease and a normal ejection fraction was observed. The patient was on the combination therapy of cobimetinib and vemurafenib for two years, escitalopram (20 mg) for a year, and mirtazapine (30 mg) for nine months. She was transferred to the Coronary Care Unit from the emergency department, where recurrent R-on-T phenomenon, TDP, and syncope were observed (Figure 2). The blood test revealed the marked hypokalemia (2.7 mg/dL), and elevated creatinine level (1.45 mg/dL), which was prevalent for the last five months.

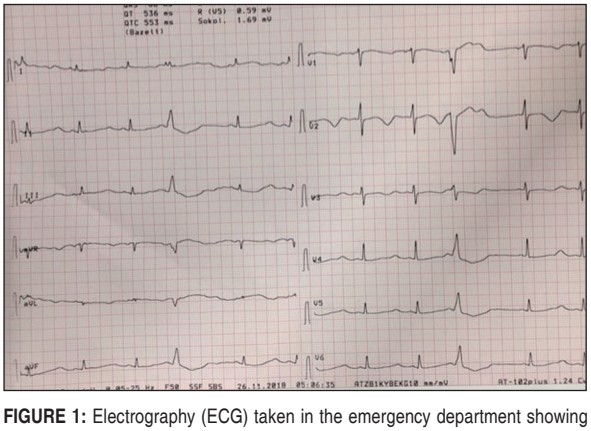

**FIGURE 1:** Electrography (ECG) taken in the emergency department showing long QT (700 ms) and frequent ventricular extrasystole.

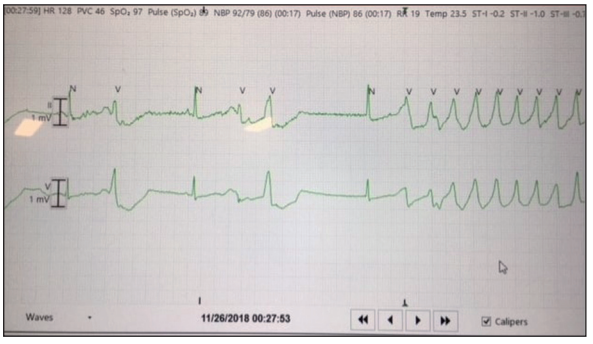


**FIGURE 2:** The rhythm stripe observed from the telemetry recording during syncope episode and showing multiple R on T phenomena and Torsade de Pointes as the cause of syncope.

Though, the patient had a three-month-old history of near syncope episode when she was prescribed ciprofloxacin for gallbladder infection. All drugs were withheld, and the patient was followed in the Coronary Care Unit for four days with continuous monitoring of heart rhythm and potassium replacement. Hypokalemia was persistent and required continuous potassium replacement. QT interval decreases from 700 to 500 ms though it was still above the normal range. For patient safety and owing to adverse effects, the drugs were discontinued, and ICD was implanted. The patient was discharged with beta-blocker and potassium replacement therapy.

## DISCUSSION

This study is based on the patient who was on vemurafenib, cobimetinib, escitalopram, and mirtazapine therapy program. Vemurafenib exhibits certain cardiac side effects, and the most common is QTc prolongation.[8] It has been mentioned in the previous study that vemurafenib is nephrotoxic, and its side-effects seem to be tubulointerstitial damage with an acute and chronic condition, further resulting in a decreased glomerular filtration rate and electrolyte imbalance, such as hypokalemia, hypocalcemia, hyponatremia, and hypophosphatemia.[9] But in this case, the patient had hypokalemia and elevated creatinine levels for five months, which could be associated with the nephrotoxic effect of vemurafenib. These adverse effects (nephrotoxicity, hypokalemia, and QTc prolongation) might contribute to the prolonged QT interval and TDP. As we know, quinolone antibiotics are also among the QTc prolonging agent,

and near syncope episodes were seen during ciprofloxacin administration. It might be due to short episodes of ventricular arrhythmias.

There is no convincing data for cobimetinib and its adverse effect as nephrotoxicity and QTc prolongation except for hypokalemia in a phase IB dose-escalation study.

The occurrence of electrocardiographic abnormalities, including QTc prolongation, has been known as a complication of acute citalopram overdose, while few data also indicate the occurrence of QTc prolongation and arrhythmia in therapeutic doses. Escitalopram is more likely to cause QTc prolongation in patients with metabolic disturbance or pre-existing cardiac disease.[10] In the reference of psychotropic drugs and ECG abnormalities, QTc prolongation and TDP have been reported in patients having a therapeutic program of mirtazapine.[11] While in this study, the patient had pre-existing metabolic disturbance, which might have contributed to QTc prolongation despite the therapeutic dose of escitalopram and mirtazapine.

Hypokalemia and prolonged QT (500 ms) persisted after the drug discontinuation, and there was persistent hypokalemia and elevated creatinine levels for the last five months. This indicates some damage (persistent if not permanent) in the kidney and cardiac electrical system. That is why the patient was discharged after ICD implantation along with beta-blocker and potassium replacement therapy.

## CONCLUSION

The combination of MEK inhibitors (cobimetinib and trametinib) and BRAF inhibitors (vemurafenib and dabrafenib) is now considered as the first-line treatment of patients with BRAF V600-mutated metastatic melanoma. Most of these patients were also on antidepressant drugs. We believe that the use of antineoplastic drugs and antidepressants concomitantly might have a synergistic effect on some fatal side-effects, like hypokalemia, QTc prolongation, and TDP. So, it is vital that these patients should have their renal function tests and ECG to be followed on a regular basis. The selection of antibiotics, antidepressants, or any other drugs should be made carefully, by properly following the latest recommended guidelines, to overcome the false drug interaction and side-effects. The discontinuation of drugs should be considered in case of fatal side-effects only.

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### *Conflict of Interest*

*No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.*

### *Authorship Contributions*

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## REFERENCES


1. Negulescu M, Deilhes F, Sibaud V, et al. Panniculitis associated with MEK inhibitor therapy: an uncommon adverse effect. Case Rep Dermatol. 2017;9(1):80-85. [Crossref] [PubMed] [PMC]
2. Fiocchi R, Gori M, Taddei F, Trevisani L, Gallo M, Eleftheriou G. Cardiac toxicity of combined vemurafenib and cobimetinib administration. Int J Clin Pharmacol Ther. 2019;57(5): 259-263. [Crossref] [PubMed]
3. Kloth JSL, Pagani A, Verboom MC, et al. Incidence and relevance of QTc-interval prolongation caused by tyrosine kinase inhibitors. Br J Cancer. 2015;112(6):1011-1016. [Crossref] [PubMed] [PMC]
4. Launay-Vacher V, Zimner-Rapuch S, Poulalhon N, et al. Acute renal failure associated with the new BRAF inhibitor vemurafenib: a case series of 8 patients. Cancer. 2014;120(14):2158-2163. [Crossref] [PubMed]
5. Teuma C, Pelletier S, Amini-Adl M, et al. Adjunction of a MEK inhibitor to vemurafenib in the treatment of metastatic melanoma results in a 60% reduction of acute kidney injury. Cancer Chemother Pharmacol. 2017;79(5): 1043-1049. [Crossref] [PubMed]
6. Lieu CH, Hidalgo M, Berlin JD, et al. A Phase Ib dose-escalation study of the safety, tolerability, and pharmacokinetics of cobimetinib and duligotuzumab in patients with previously treated locally advanced or metastatic cancers with mutant KRAS. Oncologist. 2017;22(9): 1024-e1089. [Crossref] [PubMed] [PMC]
7. Sala M, Coppa F, Cappucciati C, et al. Antidepressants: their effects on cardiac channels, QT prolongation and torsade de pointes. Curr Opin Investig Drugs. 2006;7(3):256-263. [PubMed]
8. Raftopoulos LG, Aggeli C, Zisimos K, et al. Cardiotoxicity after vemurafenib administration. Hellenic J Cardiol. 2019;60(4):256-257. [Crossref] [PubMed]
9. Jhaveri KD, Sakhiya V, Fishbane S. Nephrotoxicity of the BRAF inhibitors vemurafenib and dabrafenib. JAMA Oncol. 2015;1(8): 1133-1134. [Crossref] [PubMed]
10. Cooke MJ, Waring WS. Citalopram and cardiac toxicity. Eur J Clin Pharmacol. 2013;69(4):755-760. [Crossref] [PubMed]
11. Goodnick PJ, Jerry J, Parra F. Psychotropic drugs and the ECG: focus on the QTc interval. Expert Opin Pharmacother. 2002;3(5): 479-498. [Crossref] [PubMed]