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# CARDIOTOXICITY INDUCED BY CAPECITABINE AND OXALIPLATIN IN GASTRIC CANCER TREATMENT: A RARE CASE OF CARDIAC ARREST AND CARDIOGENIC SHOCK

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## ABSTRACT

*Introduction:* Combination-based adjuvant chemotherapy utilising capecitabine and oxaliplatin is widely used in gastric cancer treatment. Rare but severe cardiac events such as prolonged QT, cardiac arrest and cardiogenic shock can result from their use.

*Case description:* A 45-year-old female with gastric adenocarcinoma was started on capecitabine-oxaliplatin chemotherapy one week before presenting to the emergency department with weakness. Blood pressure was 78/56 mmHg, heart rate 140 bpm and oxygen saturation 85%. She became unresponsive with pulseless ventricular fibrillation; CPR was initiated with immediate intubation. She received two shocks with a return of spontaneous circulation. Laboratory tests revealed serum potassium (3.1 mmol/l), magnesium (1.1 mg/dl) and troponin (0.46 ng/ml). An EKG revealed sinus tachycardia with a prolonged QT interval (556 ms). The combined effects of capecitabine, oxaliplatin and electrolyte abnormalities likely contributed to the QT prolongation. An echocardiogram demonstrated an ejection fraction of 10%–15%. An emergent right-heart catheterisation showed right atrial pressure of 10 mmHg and pulmonary artery pressure of 30/18 mmHg; cardiac output and index were not recorded. An intra-aortic balloon pump was placed, and she was admitted to the ICU for cardiogenic shock requiring norepinephrine, vasopressin and dobutamine. A repeat echocardiogram showed a significantly improved ejection fraction of 65%, and she was discharged.

*Discussion:* Capecitabine and oxaliplatin cardiotoxicity is an exceedingly rare occurrence, with both drugs reported to cause QT prolongation.

*Conclusion:* Healthcare providers must recognise the QT prolongation effects of capecitabine and oxaliplatin, leading to life-threatening cardiac arrhythmias.

## KEYWORDS

Oxaliplatin, capecitabine, QT prolongation, cardiogenic shock

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## LEARNING POINTS

- Recognise the QT-prolonging effects of capecitabine and oxaliplatin-based chemotherapy.
- Recognise that cardiogenic shock and cardiac arrest with capecitabine and oxaliplatin-based chemotherapy can occur in individuals with benign cardiac history, especially early in treatment.

## INTRODUCTION

Combination-based adjuvant chemotherapy utilising capecitabine and oxaliplatin has become a standard approach in gastric cancer treatment. Rare but severe cardiac events, such as prolonged QT, cardiac arrest and cardiogenic shock can result from their use.

## CASE DESCRIPTION

A 45-year-old female with stage II B gastric adenocarcinoma was started on capecitabine-oxaliplatin chemotherapy one week before presenting to the emergency department with weakness. Initial blood pressure (BP) was 78/56 mmHg, heart rate was 140 bpm and oxygen saturation was 85%. Within minutes of the presentation, she became unresponsive with pulseless ventricular fibrillation. CPR was initiated for cardiac arrest, and she required immediate intubation. She received two shocks, and epinephrine and amiodarone administration, with the return of spontaneous circulation. Laboratory tests revealed serum potassium of 3.1 mmol/l, magnesium of 1.1 mg/dl, troponin 0.46 ng/ml, creatinine 1.74 mg/ml, AST/ALT 2990/1567 IU/l and lactic acid 12 mEq l. An EKG revealed sinus tachycardia with a prolonged QT interval of 556 ms, as shown in *Figure 1*.

The combined effects of capecitabine, oxaliplatin and electrolyte abnormalities likely contributed to the QT prolongation. An echocardiogram demonstrated an ejection fraction of 10%–15% with extensive wall motion abnormalities, as shown in *Figures 2 and 3*.

An emergent right-heart catheterisation showed right atrial pressure of 10 mmHg and pulmonary artery pressure of 30/18 mmHg; however, cardiac output and index were not recorded. An intra-aortic balloon pump was placed. The patient was admitted to the ICU for treatment of cardiogenic shock requiring norepinephrine, vasopressin and dobutamine, which were gradually weaned off with the removal of the IABP. A repeat echocardiogram one week later showed a significantly improved ejection fraction of 65% with resolution of the wall motion abnormalities, and she was discharged home.

## DISCUSSION

Capecitabine, a fluoropyrimidine and a prodrug of 5-fluorouracil (5-FU), inhibits thymidylate synthase preferentially within tumour cells, depleting the tumour of thymine stores and halting cellular reproduction. Oxaliplatin is an alkylating agent that cross-links and hinders DNA-associated proteins, stopping reproduction. These two medications are commonly utilised together (known as CAPOX or XELOX) in treating colorectal and gastric neoplasms. Although common side effects of this combination include myelosuppression, alopecia, gastrointestinal ulcers, hearing loss and nephrotoxicity, cardiotoxicity is relatively rare. One study proposed that capecitabine and 5-FU have a similar cardiotoxicity rate of 1%–18%[1,2].

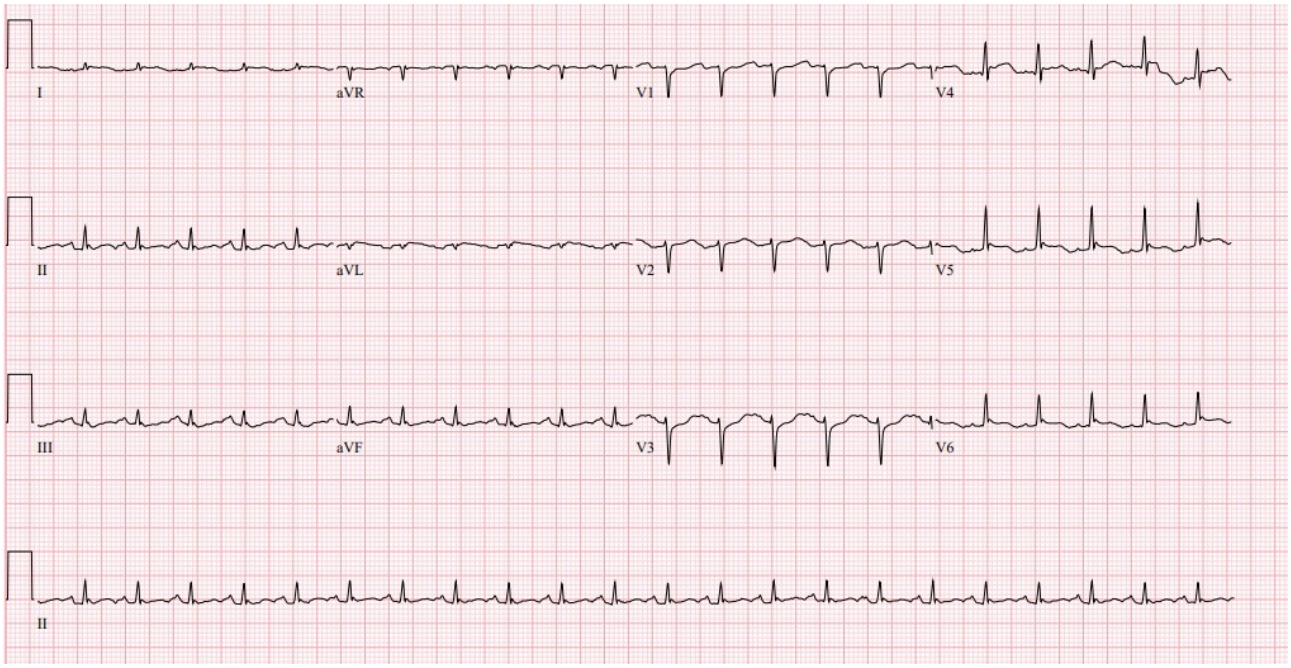


*Figure 1. EKG showing sinus tachycardia with a prolonged QT interval of 556 ms, low voltage QRS and non-specific T-wave abnormality.*

Although uncommon, previously proposed mechanisms to explain the cardiotoxic properties of fluoropyrimidines such as capecitabine, include protein kinase c-mediated vasospasm of coronary arteries[3,4], myocardial ischaemia, destruction of cardiomyocytes via oxidative stress and QT prolongation[5]. These mechanisms are more likely to contribute to cardiogenic shock in a patient with underlying cardiac disease[6]. Other factors associated with increased relative risk included concomitant etoposide, calcium channel blockers or nitrate use[6]. It may be difficult to predict risk accurately; however, these are essential factors to consider when discussing treatment options.

As in the case of the patient in this report, few studies have shown that cardiogenic shock following capecitabine can manifest in those with previously benign cardiac histories[4,7]. Muco et al. published a case report on a 32-year-old woman who received three days of capecitabine following neoadjuvant chemotherapy with carboplatin/paclitaxel, bilateral mastectomy and radiation therapy for invasive ductal carcinoma of the breast[4]. She presented to the ED in cardiac arrest with a workup initially concerning Brugada syndrome vs. anterolateral lead STEMI. However, further management, including cardiac catheterisation and a chest CT scan, failed to demonstrate any significant disease. There was no family history of cardiac problems. She had a prolonged QTc of 504 ms on the initial EKG, and a repeat EKG showed resolution of the initial ST-elevation changes.

Further questioning from the family revealed that after starting capecitabine, she had "burning chest pain". Her hospital stay was complicated by an anoxic neurological injury precipitating a status epilepticus refractory to sedating and anti-convulsive treatment. She was ultimately discharged home to a long-term care facility with incomplete return of neurological function[4]. Hayasaka et al. reported a case of a 39-year-old woman with ascending colon cancer on capecitabine 3,600 mg/day following a right hemicolectomy and lymph node dissection[5]. After the third round of chemotherapy, she experienced light-headedness and collapsed into cardiopulmonary arrest. Following resuscitation, an EKG on ER admission revealed a prolonged QT (482 ms) in the absence of any organic heart disease. Family history of sudden cardiac death and genetic mutation workup for congenital long QT syndrome was also negative. Cessation of capecitabine was associated with fusion of TU waves and gradually shortened QT interval (442 ms) four days later. Since cardiopulmonary defibrillator placement, the patient has not had any prolonged QT, ventricular contractions or ventricular fibrillation for at least four years[5]. These case studies highlight some similarities to our report, including the patient's age, gender, cardiac symptoms before fulminant cardiac arrest and prolonged QT interval – all in the setting of unremarkable personal and family cardiac histories.

As mentioned by Hayasaka et al., there may be a multifactorial genetic relationship between capecitabine metabolism and predisposition to symptoms from QT prolongation[5]. Three

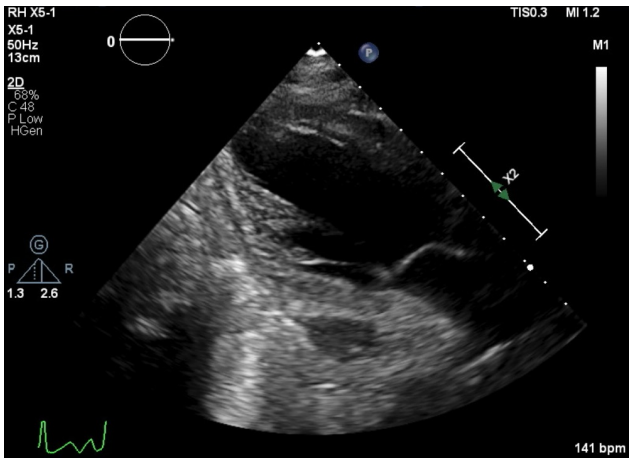


*Figure 2. Parasternal long axis view, visualised ejection fraction 10%–15%.*

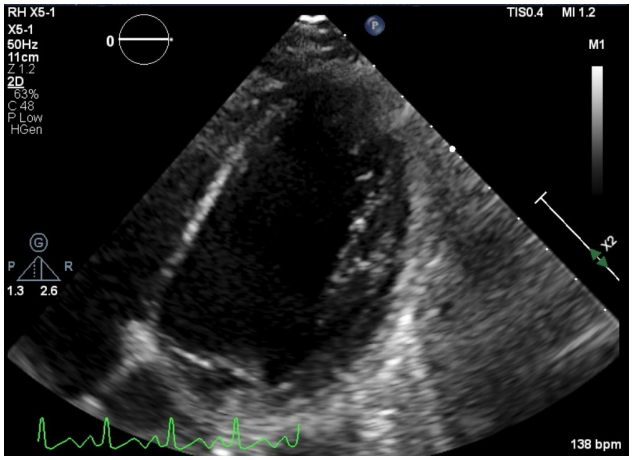


*Figure 3. Apical four-chamber view.*

enzymes known to metabolise capecitabine to 5-FU include carboxylesterase, cytidine deaminase (CDA) and thymidine phosphorylase. Genetic polymorphisms in these enzymes may exist, leading to potentially elevated levels of circulating 5-FU if the mutation yields an overactive enzyme[5]. About one-third carry congenital mutations in individuals with acquired long QT syndrome[6]. As suggested by Itoh et al., identifying cardiotoxicity risk in these individuals with a control EKG (>440 ms), presence of cardiac symptoms and age <40 years would be helpful[6]. Given the variety of potential cardiotoxic mechanisms from capecitabine use, a reasonable recommendation proposed by Hayasaka et al. would be to perform serial EKGs during the first few days or weeks of treatment[5].

Capecitabine-induced cardiotoxicity has gained more recognition in the last two decades with the publication of several case reports, but there is limited data on the effects of oxaliplatin. In mice, oxaliplatin has been shown to derange energy metabolic pathways in cardiomyocytes, ultimately increasing glycolysis rates and lactate production, resulting in focal areas of necrosis with neutrophil infiltration[8]. In recent years, a few case reports on patients solely on oxaliplatin have shown that the medication can cause acute coronary vasospasm mimicking a STEMI[9] and third-degree atrioventricular block[10]. In 2015, oxaliplatin was added to

the CredibleMeds database list of drugs that can cause QT prolongation and Torsades de Pointes.

## CONCLUSION

The patient in this report was on a capecitabine-oxaliplatin combination regimen for one week before the onset of QT prolongation and shock. It is difficult to pinpoint the precise culprit of the adverse event. Still, given that both chemotherapy medications are known to be cardiotoxic occasionally, it is reasonable to suspect a synergistic effect. More research is needed to determine if adverse cardiac events are more common when on one or both capecitabine and oxaliplatin.

Capecitabine and oxaliplatin cardiotoxicity is an exceedingly rare occurrence. Although infrequent, both drugs have been reported to cause QT prolongation. Healthcare providers must recognise the potential QT interval prolongation effects of capecitabine and oxaliplatin, leading to potentially life-threatening cardiac arrhythmias.

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