

Capecitabine-induced ventricular fibrillation arrest: Possible Kounis syndrome

Kazuhiko Kido¹, Val R Adams², Richard S Morehead³ and Alexander H Flannery^{1,2}

Abstract

We report the case of capecitabine-induced ventricular fibrillation arrest, possibly secondary to type I Kounis syndrome. A 47-year-old man with a history of T3N1 moderately differentiated adenocarcinoma of the colon, status-post sigmoid resection, was started on adjuvant capecitabine approximately five months prior to presentation of cardiac arrest secondary to ventricular fibrillation. An electrocardiogram (EKG) revealed ST segment elevation on the lateral leads and the patient was taken emergently to the cardiac catheterization laboratory. The catheterization revealed no angiographically significant stenosis and coronary artery disease was ruled out. After ruling out other causes of cardiac arrest, the working diagnosis was capecitabine-induced ventricular fibrillation arrest. As such, an inflammatory work up was sent to evaluate for the possibility of a capecitabine hypersensitivity, or Kounis syndrome, and is the first documented report in the literature to do so when evaluating Kounis syndrome. Immunoglobulin E (IgE), tryptase, and C-reactive protein were normal but histamine, interleukin (IL)-6, and IL-10 were elevated. Histamine elevation supports the suspicion that our patient had type I Kounis syndrome. Naranjo adverse drug reaction probability scale indicates a probable adverse effect due to capecitabine with seven points. A case of capecitabine-induced ventricular fibrillation arrest is reported, with a potential for type I Kounis syndrome as an underlying pathology supported by immunologic work up.

Keywords

Capecitabine, Kounis syndrome, ventricular fibrillation, cardiac arrest

Introduction

Capecitabine is an orally available pro-drug converted to 5-fluorouracil (5-FU) within tumor tissue which has FDA-approved indications for metastatic colorectal and breast cancer.¹ Cardiotoxicity due to 5-FU or its derivatives is well recognized.^{2,3} Clinical manifestations of angina, acute coronary syndrome, arrhythmias, myocarditis, and heart failure are recognized as presentations of 5-FU cardiotoxicity.² Coronary vasospasm due to capecitabine has been reported and is believed to play a major role contributing to the toxicity.^{4–7} The mechanism behind 5-FU and derivatives inducing coronary vasospasm remains widely debated and among other explanations, includes accumulation of toxic metabolites and allergic reactions.² There are case reports of ventricular arrhythmia due to capecitabine combination therapy with irinotecan or oxaliplatin.^{8,9}

There is only one published case report of ventricular arrhythmia and cardiac arrest by monotherapy with capecitabine.¹⁰ This report, or any others in the literature reporting on 5-FU cardiac events, has not evaluated a hypersensitivity work-up. Clarifying the mechanism of this cardiotoxicity, possibly due to a hypersensitivity reaction, carries important implications. We report the first published case of

¹Department of Pharmacy Services, University of Kentucky HealthCare, Lexington, KY, USA

²Department of Pharmacy Practice and Science, University of Kentucky College of Pharmacy, Lexington, KY, USA

³Division of Pulmonary, Critical Care, and Sleep Medicine, University of Kentucky HealthCare, Lexington, KY, USA

Corresponding author:

Kazuhiko Kido, University of Kentucky HealthCare, 800 Rose Street, H-110, Lexington, KY 40502, USA.

Email: kazuhiko.kido0322@gmail.com

capecitabine-induced ventricular fibrillation and cardiac arrest that is supported by a cardiac hypersensitivity work up.

Case report

A 47-year-old man with a history of T3N1 moderately differentiated adenocarcinoma of the colon, status-post sigmoid resection, was started on adjuvant capecitabine approximately five months prior to presentation of cardiac arrest secondary to ventricular fibrillation.

In addition to colon cancer, the patient's past medical history was also significant for hypertension, obesity, and sleep apnea. Family history was pertinent for a fatal myocardial infarction (father, age 63) and chronic obstructive pulmonary disease (mother). The patient had no known drug allergies. His medications prior to admission included: capecitabine 1600 mg twice daily (1264 mg/m²/day), hydrochlorothiazide 25 mg daily, ibuprofen 400–800 mg as needed, ondansetron 8 mg as needed, and vitamin D 1000 International Units daily. The patient was completing his 8th cycle of capecitabine therapy. The last dose of capecitabine was taken the evening prior to admission. Smoking, alcohol, and other illicit drug use were denied.

Although exact accounts vary, the patient and his wife may have been engaging in some sort of sexual activity on the day of admission. Per her account, the patient was previously normal, then his eyes rolled back

in his head, he made several intermittent gasping and gurgling noises, and had slight shaking of his shoulders and upper extremities. The patient had never experienced events like this before, nor was there a family history of seizure. Other than nausea that was well controlled with ondansetron, the patient had not been experiencing any sick symptoms prior to this episode and had never experienced any cardiac issues, including palpitations or syncope. These shaking movements lasted until Emergency Medical Services (EMS) arrived. Initial rhythm at the scene was ventricular fibrillation. Cardiopulmonary resuscitation was performed by EMS and the patient was intubated and transferred to our intensive care unit. Return of spontaneous circulation was achieved.

An electrocardiogram (EKG) revealed ST segment elevation on the lateral leads (Figure 1) and the patient was taken emergently to the cardiac catheterization laboratory. The catheterization revealed no angiographically significant stenosis and coronary artery disease was ruled out. The patient was managed with therapeutic hypothermia and sent to computed tomography (CT) scanner to evaluate head bleed as a possible explanation for ST segment elevation. Although the CT revealed some concern for a minor hemorrhage, an MRI revealed no intracranial abnormalities, including neither hemorrhage nor signs of anoxic injury. Chest radiography revealed an infiltrate and with a compatible clinical picture, the patient was started on

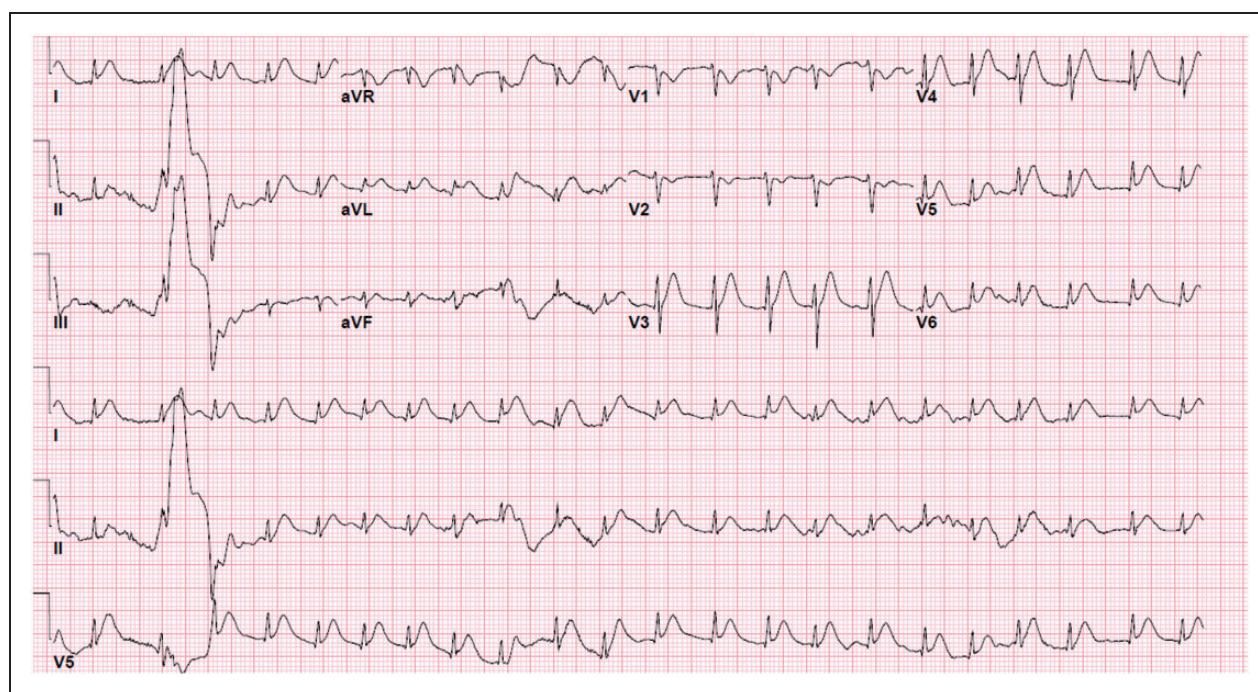


Figure 1. Electrocardiogram (EKG) upon admission.

azithromycin, ceftriaxone, and metronidazole for a community acquired and/or aspiration pneumonia. A CT pulmonary embolus (CT PE) protocol was performed and was negative for PE, but suggested a bilateral pneumonia.

A video electroencephalogram (vEEG) was performed that demonstrated bifrontal sharps, which may indicate mild hypoxic injury that does not appear on imaging and may make the patient more susceptible to seizures. The patient was started on levetiracetam and remained seizure-free for the remainder of the hospital stay.

The patient's creatine kinase (CK) and CK MB were within normal limits upon arrival. The initial troponin I was 0.02 ng/mL, which peaked at 0.29 ng/mL later that afternoon. The initial lactate was 2.2 mmol/L, which peaked at 2.8 mmol/L the evening of admission. The patient had an elevated anion gap of 20 mmol/L upon admission with liver enzymes approximately two times higher than upper normal range. With the exception of the anion gap, slightly elevated glucose, and SCr of 1.3 mg/dL, the patient's basic metabolic panel (BMP) was within normal limits. The patient's low density lipoprotein (LDL) was 54 mg/dL. All of the laboratory abnormalities were thought to be consequences of ventricular fibrillation arrest, and quickly declined to normal values beginning the day after admission.

The day after admission the patient experienced an episode of supraventricular tachycardia that resolved with administration of magnesium. A formal two-dimensional transthoracic echocardiogram revealed

mildly reduced left ventricular (LV) systolic function with an ejection fraction of 40–50% with mild global hypokinesis of the LV and moderate concentric LV hypertrophy. The right ventricle (RV) was mildly dilated with mildly reduced systolic function. The estimated RV systolic pressure was mildly elevated at 35–40 mm Hg. Trace aortic regurgitation was also seen.

After ruling out other causes of cardiac arrest, the working diagnosis was capecitabine-induced ventricular fibrillation arrest. As such, an inflammatory work up was sent to evaluate for the possibility of a capecitabine hypersensitivity per previously published recommendations.¹¹ Due to lab collection, immunoglobulin E (IgE), tryptase, interferon gamma, tumor necrosis factor alpha (TNF- α), and histamine were not able to be drawn until 56 h post-admission. These laboratory values are noted in Table 1.

The patient was extubated 72 h following admission, at which time a 12-lead EKG revealed a normal EKG with no abnormalities (Figure 2). The patient was later transferred to the floor and spent a total of nine days hospitalized. He was discharged directly home with instructions to discontinue capecitabine therapy. In the follow up clinic visit, computerized axial tomography showed nodules in his peritoneal cavity and later positron-emission tomography scan confirmed metastatic adenopathy. His diagnosis was advanced to stage IV. Kras mutation was found to be negative. He was placed on oxaliplatin, irinotecan, and bevacizumab in place of capecitabine therapy and has tolerated the first three cycles well.

Table 1. Hypersensitivity work-up.

	Lab value	Reference value	Time since admission (hour)
Total IgE	8	<114 kU/L	56
Specific IgE to administered drug	Unavailable	N/A	N/A
Cardiac enzymes and troponins			
CK-MB	1.3 ng/mL	0–5.0 ng/mL	On admission
Troponin I	0.29 ng/mL (peak)	0.00–0.04 ng/mL	13.5
Tryptase	<1 ng/mL	2–10 ng/mL	56
Histamine	32 nmol/L	0–8 nmol/L	56
Prostaglandin D2	55 pg/mL	35–115 pg/mL	8.5
CRP	0.1 mg/dL	0–0.9 mg/dL	2.5
Tissue factor	Unavailable	N/A	N/A
TNF- α	<5 pg/mL	≤21 pg/mL	56
Interferon gamma	<5 pg/mL	≤4 pg/mL	56
IL-10	25.8 pg/mL	<9.2 pg/mL	8.5
IL-6	37.2	0.31–5 pg/mL	8.5

CK-MB: creatine kinase MB; CRP: C-reactive protein; IgE: immunoglobulin E; IL: interleukin; N/A: not available; TNF- α : tumor necrosis factor alpha.

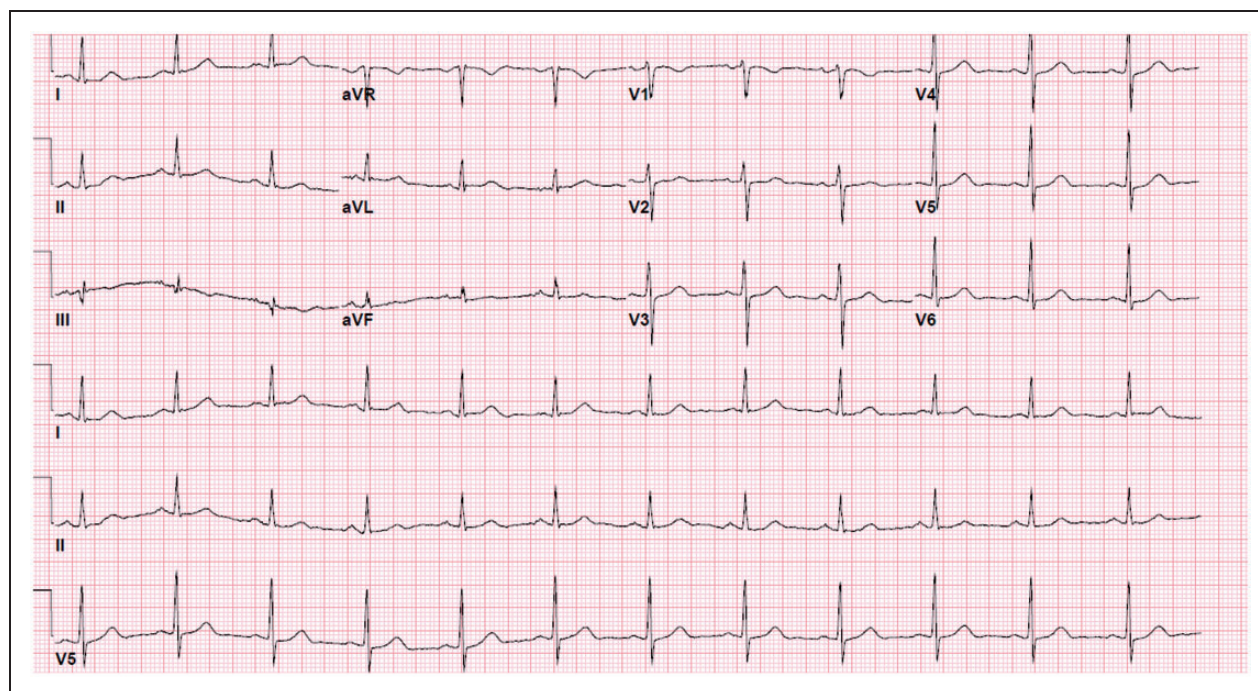


Figure 2. Electrocardiogram (EKG) upon 72 h after cardiac arrest.

Discussion

Shah et al.¹⁰ reported the first case of capecitabine-induced ventricular fibrillation and cardiac arrest. Kounis et al.¹¹ commented to discuss the possibility of this case's diagnosis not as a direct cardiotoxicity but rather as Kounis syndrome. In 1991, Kounis et al. published the case of histamine-induced coronary artery spasms.¹² Later, Kounis syndrome was defined as "the concurrence of acute coronary syndromes such as coronary spasm, acute myocardial infarction, and stent thrombosis, with conditions associated with mast-cell and platelet activation involving interrelated and interacting inflammatory cells in the setting of allergic or hypersensitivity and anaphylactic or anaphylactoid insults".¹³ This syndrome is believed to be mediated by inflammatory substances such as histamine, tryptase, cytokines, and chemokines.¹³ Three types of Kounis syndrome have been proposed.¹⁴ Type I variant includes the patient with no abnormal coronary arteries and predisposing factors for coronary artery disease. The acute release of inflammatory substances causes vasospasm either without increases in cardiac enzymes and troponins or with coronary artery spasm progressing to acute myocardial infarction with elevation of cardiac enzymes. Type II variant occurs only in patients with pre-existing atherosclerotic disease. Coronary artery spasm or plaque rupture inducing acute myocardial infarction has been reported.¹³ Type III variant was also recently described involving coronary artery stent thrombosis.¹³

The previously reported case in the literature of ventricular fibrillation arrest with capecitabine monotherapy was a 28-year-old male with no known cardiovascular risk factors or illicit drug use who presented during his 5th cycle of capecitabine therapy for metastatic colorectal cancer.¹⁰ Following emergency resuscitation, spontaneous circulation was restored and he was taken to urgent coronary angiography due to ST elevations in the 12-lead EKG. Angiography found normal coronary arteries. Troponin I was elevated at 0.23 ng/mL. In our case, the patient was also well into his treatment course with capecitabine therapy presenting during the 8th cycle of capecitabine therapy. Like the previous case, he did not have any known cardiovascular risk factors or any history of arrhythmias. Despite ST elevations, coronary angiography also showed normal coronary arteries. Troponin I was also elevated at 0.29 ng/mL. Both cases indicate a similar clinical course and manifestations. Suspecting a possible immunological pathology, an allergic work up was undertaken to evaluate an immune pathology in the cardiac toxicity of capecitabine. This is the first documented case of an allergic work up with a cardiovascular toxicity of chemotherapy.

The elevated histamine level supports the suspicion that our patient had type I Kounis syndrome. It is known that cardiac mast cell-mediated histamine release can lead to vasoconstriction in coronary arteries.¹⁵ The arrhythmogenic effects of histamine, including a reduction in the ventricular fibrillation threshold, have also been well documented.¹⁶

Although it has been postulated that elevated levels of tryptase are observed in Kounis syndrome, the tryptase level was normal for our patient. A number of potential reasons explain this phenomenon. There was not enough blood to add on tryptase to admission labs. Thus the level was delayed and may have been within normal range due to its short half-life of about 90 min.¹⁷ It has been suggested that the best time to obtain tryptase levels is 1–2 h after the event.¹⁷ Furthermore, histamine and tryptase levels have not been found to necessarily correlate in patients presenting with allergic reactions. The elevated histamine, but not tryptase level, may indicate basophil involvement and represent a late-phase allergic response.¹⁸ As a result, this case may have presented as a ‘delayed Kounis syndrome’, of which two cases have been described in the literature.^{19,20}

The cytokine profile of this case is complicated by cardiac arrest as well as the fact that the patient was cooled with therapeutic hypothermia and rewarmed, a phenomenon known to influence cytokine profiles.^{21,22} Interleukin (IL)-6 levels have been demonstrated to be elevated in therapeutic hypothermia following cardiac arrest, explaining the elevated level of IL-6 in our case.^{21,22} We hypothesize the elevated levels of IL-10 correspond to an anti-inflammatory response to the immunologic profile described in this case.

Based on the Naranjo adverse drug reaction probability scale, cardiac arrest secondary to capecitabine was probable with seven points.²³ No concentration of capecitabine was measured and the patient has never tried any other chemotherapy agents before. Our case represents the first cardiac hypersensitivity work up reported alongside a clinically suspected Kounis syndrome and provides important insights into possible immunologic mechanisms.

In the absence of other causes of ventricular fibrillation arrest or other forms of cardiac insult, an immune response to medications must not be ruled out, as was potentially the case of our patient who presented with possible type I Kounis syndrome. Increasing recognition of this phenomenon may be helpful, and hydrocortisone and H1 and H2 histamine antagonists are recommended as potential treatment options.¹³ Identifying immunologic pathologies is not only important for recommending treatment options during acute events, but for potential screening during cycles of chemotherapy as well.

Conclusion

A case of capecitabine-induced ventricular fibrillation arrest is reported, with a potential for type 1 Kounis syndrome as an underlying pathology supported by immunologic work up.

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Conflict of interest

The authors do not have any conflicts of interest to disclose.

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