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CASE SERIES
Heart failure

Capecitabine-mediated heart failure in colorectal cancer: a case series

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Background Capecitabine is a pyrimidine antimetabolite that inhibits thymidylate synthase and is commonly used in the treatment of colorectal cancer. Adverse cardiac side effects are reported in 1–18% of patients receiving Capecitabine. The most commonly proposed mechanism of cardiotoxicity in the setting of Capecitabine use is vasospasm of the coronary arteries. However, cardiotoxicity can also present as an acute coronary syndrome, arrhythmia, hypertension, and/or sudden cardiac death. Profound non-vasospastic cardiotoxicity is rare.

Case summary We describe two cases of acute heart failure leading to cardiogenic shock in patients shortly after exposure to Capecitabine. Both patients did not demonstrate the characteristic transient ST elevation seen in patients with coronary artery vasospasms secondary to Capecitabine. Both patients required admission to the Acute Cardiac Care Unit requiring vasopressor and inotropic support. Thorough diagnostic investigations including echocardiography, cardiac magnetic resonance imaging, and cardiac computed tomography did not identify infarction, myocarditis, or any infiltrative process to explain their symptoms. Both patients had complete resolution of cardiac function, with no long-term sequalae.

Discussion In patients receiving Capecitabine, reversible heart failure leading to cardiogenic shock should be considered as a potential cardiotoxic side effect.

Keywords Heart failure • Cardiogenic shock • Capecitabine • Cardiotoxicity • Cardio-oncology • Case report

Learning points

- Cardiotoxicity is a rare side effect of capecitabine chemotherapy, most commonly secondary to coronary artery vasospasm.
- Acute heart failure leading to cardiogenic shock is a rare form of cardiotoxicity that should be considered in patients on capecitabine.

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Introduction

Capecitabine is the oral pro-drug of 5-Fluorouracil (5-FU) and is a pyrimidine antimetabolite that inhibits thymidylate synthase.[1] Fluoropyrimidine-based chemotherapy is a vital aspect of the treatment of colorectal cancer. Side effects of fluoropyrimidine therapy may include myelosuppression, mucositis, nausea, emesis, diarrhoea, palmar-plantar erythrodysesthaesia, and rarely cardiotoxicity.[2,3] Cardiotoxicity can present as an acute coronary syndrome, arrhythmia, hypotension, cardiogenic shock, cardiac arrest, and/or sudden cardiac death.[2] The most commonly proposed mechanism of cardiotoxicity in the setting of Capecitabine is vasospasm of the coronary arteries. There is pre-clinical[4] and clinical[5] data that suggests that 5-FU causes vasospasm in a dose–dependent manner. Profound non-vasospastic cardiotoxicity is rare. We describe two cases of acute heart failure leading to cardiogenic shock in patients shortly after exposure to Capecitabine.

Timeline

Time	Event
Patient 1	
Day 1	Started neoadjuvant chemotherapy with Capecitabine and Oxaliplatin (CAPOX).
Day 7	Presented to Urgent Care with nausea, vomiting, weakness, shortness of breath, and pleuritic chest discomfort. Transthoracic echocardiogram (TTE) demonstrated a reduced left ventricular ejection fraction (LVEF) of <20%.
Day 7–23	Admission to Acute Cardiac Care Unit for inotropic support with milrinone.
Day 21	Repeat TTE demonstrated complete resolution of cardiac function.
Day 29	Discharged from hospital.
Day 36	Started on Raltitrexed and Oxaliplatin for management of rectal cancer.
Two months later	Cardiac computed tomography demonstrated no evidence of obstructive coronary artery disease.
Patient 2	
Day 1	Started adjuvant chemotherapy with CAPOX
Day 2	Patient experienced two episodes of central chest pain while at rest with associated diaphoresis.
Day 3	Presented to Emergency Department due to increased chest pain and profound fatigue. Patient was tachycardic and hypotensive, unresponsive to fluids. Patient was found to have grossly reduced LVEF on point of care ultrasound.
Day 3–6	Admitted to Acute Cardiac Care Unit with cardiogenic shock requiring vasopressor and inotropic support with norepinephrine and milrinone.
Day 4	TTE revealed LVEF <20% with severely depressed right ventricular systolic function.
Day 5	Coronary angiography revealed no obstructive coronary artery disease.
Day 6	Patient weaned off norepinephrine and milrinone, transferred to Cardiology Ward.
Day 8	Cardiac magnetic resonance imaging (MRI) demonstrated LVEF of 32% with a hypokinetic left ventricle, with no evidence of myocarditis, infarction, or an infiltrative process.
Day 9	Discharged from hospital.
Four months later	Repeat cardiac MRI showed significant improvement of LVEF to 59%.

Case presentations

Patient 1

A 32-year-old woman, with no personal or family history of cardiac disease, underwent a diverting ostomy for an obstructing rectal cancer. Staging revealed a clinical T4N2M1 moderately differentiated adenocarcinoma. She was started on neoadjuvant chemotherapy with Capecitabine and Oxaliplatin [CAPOX; Oxaliplatin (130 mg/m^2) on Day 1, and oral Capecitabine twice daily (1000 mg/m^2) on Days 1–14 of a 3 weeks cycle]. On Day 7 of Cycle 1, she presented with nausea, vomiting, weakness, shortness of breath, and pleuritic chest discomfort.

In Urgent Care, she was afebrile with a blood pressure of 100/71 mmHg and a heart rate of 140–160 b.p.m. Her respiratory rate was 18 with an oxygen saturation of 100% on room air. She appeared unwell and pale but was alert and oriented. Cardiac examination revealed normal heart sounds, with no murmurs or extra heart sounds. Jugular venous pressure (JVP) was elevated and there was no peripheral oedema. On respiratory exam, there was decreased air entry posteriorly with crackles to the mid thorax bilaterally. Laboratory investigations revealed a white blood count (WBC) of 16.9 $\times$ 10^9/L, haemoglobin 99 g/L, sodium of 131 mmol/L, and potassium of 3 mmol/L. The patient had a mildly elevated high-sensitivity troponin T (hsTnT) at 39 (0–14 ng/L). Chest X-ray revealed pulmonary oedema. An electrocardiogram (ECG) demonstrated sinus tachycardia with T-wave inversion laterally and non-specific ST changes (*Figure 1A*). A venous blood gas revealed a pH 7.44, pO_2 32 mmHg, bicarbonate 25 mmol/L, pCO_2 38 mmHg, and lactate 2.4 mmol/L. Once the patient was haemodynamically stable, she received diuresis for management of pulmonary oedema. Her tachycardia and dyspnoea did not improve despite diuresis, and her lactate continued to increase to 4.1 mmol/L. A transthoracic echocardiogram (TTE)

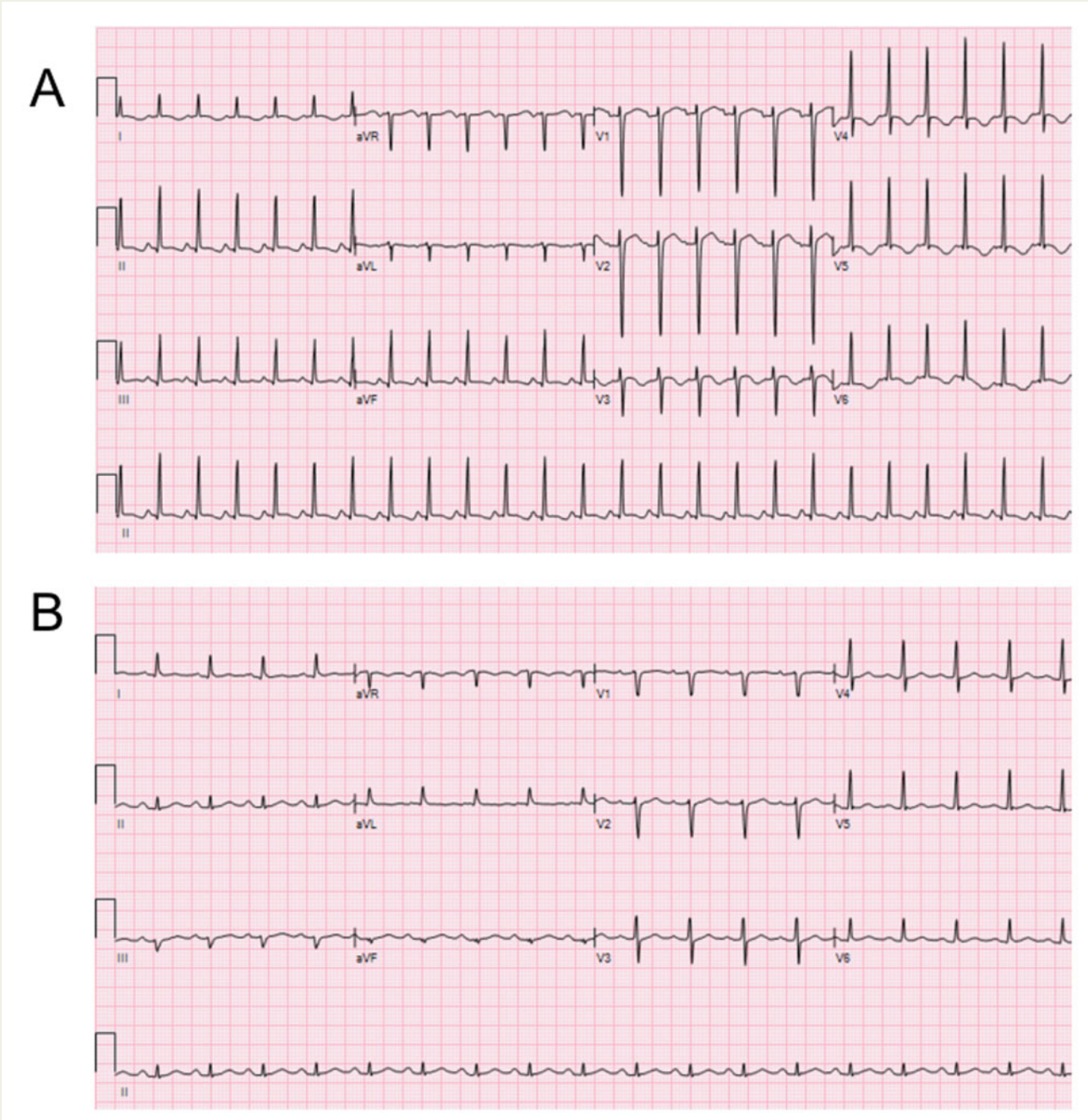

Figure 1 (*A*) Patient 1: a 12-lead electrocardiogram demonstrating sinus tachycardia with non-specific ST changes. (*B*) Patient 2: a 12-lead electrocardiogram demonstrating sinus tachycardia.

demonstrated a significantly reduced left ventricular ejection fraction (LVEF) of <20% on the apical four-chamber view following the administration of definity for left ventricular opacification (*Figure 2A*).

The patient was diagnosed with cardiogenic shock secondary to cardiomyopathy of unknown cause. She was admitted to the Acute Cardiac Care Unit for inotropic support with milrinone and haemodynamic monitoring. Infectious causes of myocarditis, including HIV, hepatitis, and parvovirus, and an autoimmune work-up were negative. Cardiac magnetic resonance (CMR) imaging on admission Day 5 showed an LVEF of 58%, LV end-diastolic volume of 104 mL, LV end-systolic volume of 43 mL, and LV stroke volume of 61 mL. Additionally, the RV volumes and RV systolic function were normal on CMR imaging. There was no evidence of delayed enhancement of the left ventricular myocardium on CMR imaging to suggest a recent infarction, myocarditis, or infiltrative process. Additionally, T1 myocardial mapping and T2 weight imaging on CMR showed no evidence of myocardial oedema.

During her admission, she had an elevated lactate for ~2 weeks and required inotropic support with milrinone for a total of 16 days. A repeat transthoracic echocardiography 14 days post-admission

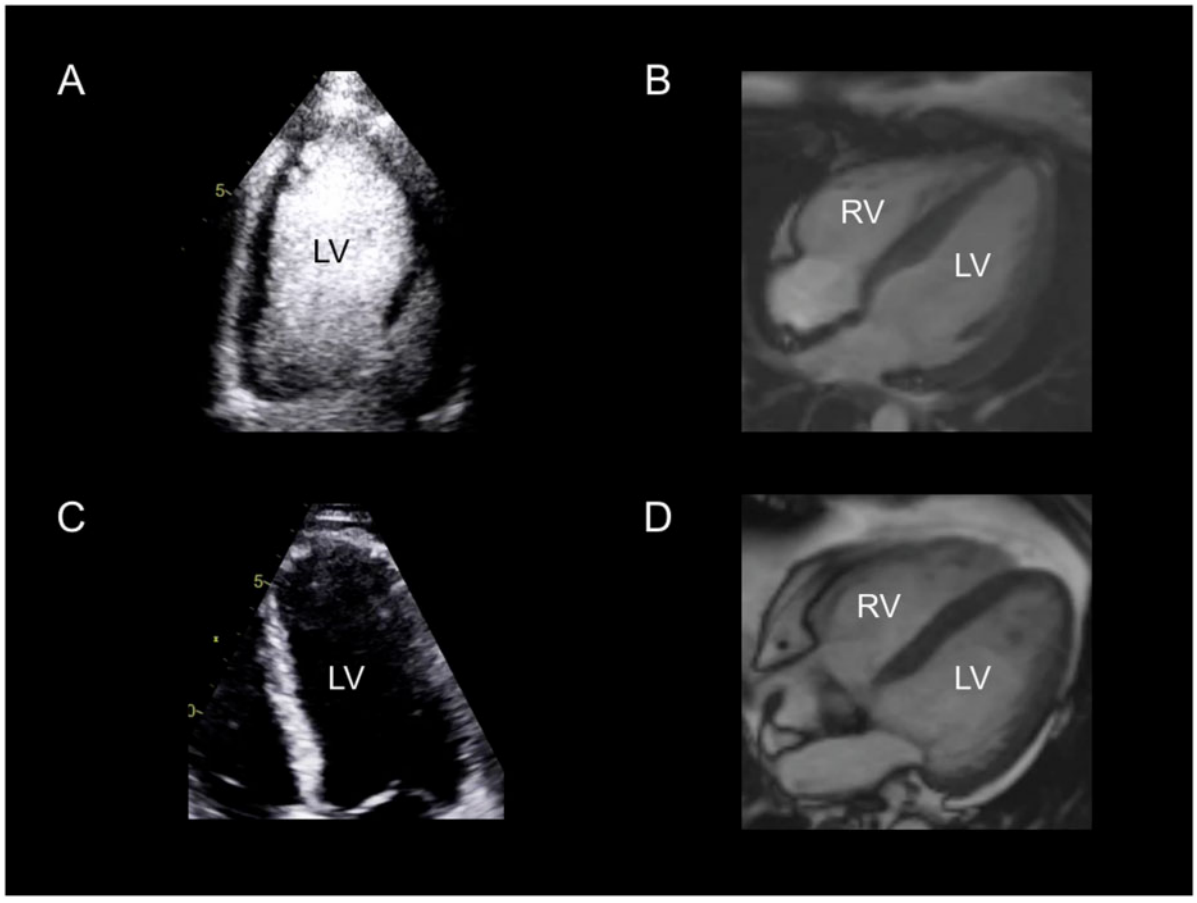

Figure 2 (*A*) Patient 1: an apical four-chamber view on transthoracic echocardiography with definity for left ventricular opacification demonstrating severe left ventricular systolic dysfunction with an left ventricular ejection fraction <20%. (*B*) Patient 1: a horizontal long-axis view on balanced steady-state free precession images demonstrating an improvement in left ventricular systolic function on inotropic support. (*C*) Patient 2: an apical four-chamber view on transthoracic echocardiography confirming severe left ventricular systolic dysfunction with a left ventricular ejection fraction <20%.(*D*) Patient 2: a horizontal long-axis view on balanced steady-state free precession images demonstrating an improvement in left ventricular ejection fraction to 32% ∼5 days after the initial transthoracic echocardiography.

demonstrated normal cardiac function, and she has successfully weaned off milrinone and discharged home on Metoprolol and Ramipril. Two months after discharge, a cardiac computed tomography scan demonstrated no evidence of obstructive coronary artery disease. She was started on Raltitrexed and Oxaliplatin for ongoing management of the rectal cancer and has experienced no further cardiotoxicity.

Patient 2

A 58-year-old functionally well man with a past medical history of hypertension, gout, and alcohol use (3–4 drinks per day), and no personal or family history of cardiac disease, presented post-operatively with a T4aN1aM0 moderately differentiated adenocarcinoma of the upper rectum. Eight weeks after low anterior resection, he received a recommendation of adjuvant CAPOX chemotherapy with chemoradiation. On Day 2 of Cycle 1, he experienced two 30-min episodes of central chest pain while at rest, associated with diaphoresis. On Day 3, his chest pain increased in severity and was associated with profound fatigue, leading him to seek medical attention.

In the emergency department, he was afebrile with a blood pressure of 91/69 mmHg, heart rate of 109 b.p.m., and oxygen saturation of 100% on room air. A cardiovascular exam revealed normal heart sounds, with no murmurs or extra heart sounds. His JVP was elevated to angle of jaw, and he had mild pitting oedema to his ankles. An ECG demonstrated sinus tachycardia and no evidence of ischaemia (*Figure 1B*). A chest X-ray revealed pulmonary oedema. His serial hsTnT measurements were 233 and 226.

A venous blood gas revealed a pH 7.38, pCO_2 38 mmHg, bicarbonate 21 mmol/L, and lactate 3 mmol/L. Point of care ultrasound demonstrated a hypokinetic left ventricle, a grossly reduced LVEF, and a dilated IVC with minimal inspiratory response. He remained hypotensive with systolic blood pressures of 80 mmHg despite resuscitation with 4 L of normal saline. He developed clinical signs of heart failure, including increasing oxygen requirements and shortness of breath. He was admitted to the Acute Cardiac Care Unit for

treatment with norepinephrine and milrinone and haemodynamic monitoring.

A formal TTE revealed an LVEF of <20% with an akinetic apex (*Figure 2B*). The right ventricular (RV) systolic function was also severely depressed with evidence of mild to moderate functional mitral regurgitation. A coronary angiogram revealed minimal coronary artery disease with no flow limiting disease. CMR imaging on admission Day 5 demonstrated an improved LVEF of 32% with a hypokinetic left ventricle, end-diastolic volume of 142 mL, end-systolic volume of 97 mL, and stroke volume of 45 mL. Additionally, T1 myocardial mapping and T2 weight imaging on CMR showed no evidence of myocardial oedema. There was no evidence of myocarditis, infarction, or infiltrative processes on CMR. He was successfully weaned off inotropic support and discharged home on Carvedilol and Ramipril after a 6-day admission.

Four months later, he underwent a repeat CMR. There was a significant improvement in the LVEF to 59%. Due to the severity of his chemotherapy-induced cardiotoxicity, he was not re-started on further fluoropyrimidine chemotherapy and proceeded with adjuvant radiation therapy alone.

Discussion

Capecitabine is a pro-drug that is catalysed by thymidine phosphorylase to fluorouracil. Thymidine phosphorylase has high expression in cancer cells, allowing for more selective accumulation of the antimetabolite in the tumour.[1] Although Capecitabine is more selective to tumour cells, the reported incidence of cardiotoxicity with Capecitabine is similar to 5-FU, occurring in 1–18% of patients.[6,7]

Some of the proposed mechanisms of cardiotoxicity due to fluoropyrimidines include coronary vasospasm,[4] myocardial ischaemia,[8] and direct toxic effect leading to oxidative stress and destruction of cardiomyocytes.[9] Cardiotoxicity can present with a range of symptoms including angina, arrhythmias, cardiogenic shock, and even sudden cardiac death.[2] Classically, patients with coronary vasospasm present similar to other causes of acute coronary syndromes, with angina, but transient ST deviation on ECG.[2,3] Coronary angiography with provocative testing can support the diagnosis of coronary vasospasm by direct visualization demonstrating no thrombus or narrowing. However, this direct visualization of vasospasm is time sensitive, due to the dose–dependent relationship of vasospasm and fluoropyrimidine cardiotoxicity.[4] Both of the cases described herein showed no evidence of regional wall motion abnormalities or obstructive coronary artery disease on cardiac imaging. Although coronary vasospasm can lead to development of cardiogenic shock, other mechanisms, such as toxic myocardial inflammation or stress cardiomyopathy, resulting in myocardial dysfunction may better explain the mechanism of cardiogenic shock in these two cases.

In both cases, non-invasive diagnostic images, including TTE and CMR, were used to confirm the presence of severe left ventricular systolic dysfunction. One limitation of our case series is the lack of myocardial biopsy, which may have provided additional information on the mechanism of cardiotoxicity. However, since there was no evidence of delayed enhancement of the left ventricular myocardium on CMR to suggest myocarditis, or an infiltrative or ischaemic process, we elected not to pursue an invasive myocardial biopsy.

Both of our patients received CAPOX chemotherapy and presented with cardiogenic shock within days of starting chemotherapy. This timeline is similar to what has been reported in a retrospective study, which demonstrated that the first occurrence of cardiotoxicity occurred within 3–6 days of starting chemotherapy.[10] In a prospective study of patients receiving 5-FU and oxaliplatin, 8.5% of patients experienced clinical symptoms of cardiotoxicity, which was associated with biochemical changes including an elevated N-terminal pro-brain natriuretic peptide and lactic acid, but not necessarily a change in global LVEF.[8] Moreover, the same study found that plasma lactic acid increases significantly during 5-FU treatment, regardless of whether the patient had symptomatic cardiotoxicity.[8] This could potentially explain the 2 weeks of elevated serum levels of lactate in Patient 1. It is also possible that the elevated lactate, in this case, was due to the continued stress on the myocardium from severe cardiac dysfunction caused by Capecitabine.

Some of the risk factors for developing cardiotoxicity to fluoropyrimidines include pre-existing cardiovascular disease, continuous infusion schedules, and concomitant cisplatin treatment.[2,10,11] Although pre-existing cardiovascular disease has been shown to significantly predispose patients to fluorouracil-associated cardiotoxicity,[10] with a relative risk of 6.83,[11] a systematic review showed conflicting results.[2] Of interest, the patient in Case 2 had predisposing cardiovascular risk factors (hypertension and alcohol use), potentially increasing his risk of cardiotoxicity from Capecitabine, despite exhibiting no exercise-limiting symptoms at baseline. For high-risk patients that require additional chemotherapy treatment, changing the agent to one with a safer cardiac profile should be considered. For example, the patient in case 1 received Raltitrexed, a quinazoline antifolate that selectively inhibits thymidylate synthase and has been shown to have outcomes similar to 5-FU in the treatment of metastatic colorectal cancer.[12] Raltitrexed appears to have a safer cardiac profile for high-risk patients who have experienced cardiotoxicity on 5-FU based regimens.[13]

Dihydropyridine dehydrogenase (DPD) is the enzyme involved in the rate-limiting catabolism of 5-FU. Dihydropyridine dehydrogenase deficiency predisposes individuals to severe 5-FU toxicity, including profound neutropenia, mucositis, diarrhoea, and vomiting.[14] In patients with DPD-deficiency, the onset of 5-FU toxicity can be rapid, sometimes even within hours of the first dose.[15] In such cases, an antidote, uridine triacetate, can be considered.[15] The patients in our case series did not present with these classic symptoms of DPD-deficiency and, therefore, DPD testing was not pursued.

Although both patients described here did not have long-term cardiac dysfunction, some patients may experience irreversible cardiac damage. When patients experience cardiotoxicity related to an anticancer agent, referral to a cardio-oncology specialist is recommended, as such an approach may result in improved cardiac optimization, higher rates of cancer treatment continuation, and ultimately improved oncologic outcomes.[16–18] Additionally, for patients who have cardiac risk factors, referral to a cardio-oncology specialist pre-chemotherapy can allow for cardiac optimization and ultimately improve completion of cancer therapy.[16]

Conclusion

In patients receiving Capecitabine, reversible heart failure and cardiogenic shock should be considered as a potential cardiotoxic side effects. Capecitabine should be promptly discontinued and patients should be managed with multidisciplinary collaboration from the disciplines of Cardiology and Oncology.

Lead author biography

Dr Erin McAndrew is an Internal Medicine resident at the University of Manitoba. She completed a Master of Science and Doctor of Medicine at the University of Manitoba. Her research interests include cardio-oncology and long-term cardiac consequence of chemotherapy.

Supplementary material

Supplementary material is available at *European Heart Journal - Case Reports* online.

Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The authors confirm that written consents for submission and publication of this case report including images and associated text have been obtained from the patients in line with COPE guidance.

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