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CASE REPORT
Heart failure

Fluorouracil-induced Takotsubo cardiomyopathy causing cardiogenic shock: a case report of clinical and acute cardiac magnetic resonance imaging features

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Background Takotsubo cardiomyopathy (TTS) is an extremely rare complication of fluorouracil containing chemotherapy regimes such as FOLFOX used for colorectal cancer, occurring in only five previous case reports. Due to its potentially fatal outcomes, yet infrequent presence in the literature, it is worthwhile reviewing the clinical features and outcomes of this phenomenon.

Case summary A 54-year-old lady was admitted with cardiogenic shock. A cardiac magnetic resonance imaging (CMR) showed mid-ventricle to apical hypokinesis and confirmed TTS. She was managed with inotropes and non-invasive ventilation after which she recovered fully both clinically and in her CMR features 6 weeks following discharge.

Discussion This is the first case showing the acute CMR features of this complication and highlights the need for awareness of this rarely occurring cardiotoxicity. It also shows the potentially fatal phenomenon can be fully reversible when diagnosed and managed promptly even in patients with metastatic cancer and critical illness.

Keywords Flourouracil • FOLFOX • Takotsubo cardiomyopathy • Cardiac MRI • Case report

Learning points

- Fluorouracil containing chemotherapy can potentially cause life-threatening Takotsubo cardiomyopathy and should be managed with intensive care support. In all previously published cases including this, it has been fully reversible even in the setting of patients with metastatic cancer.
- Acute use of cardiac magnetic resonance imaging can make the diagnosis and can avoid the need for invasive coronary angiography and its incumbent complications.

Introduction

Fluorouracil chemotherapy has been associated with various forms of cardiotoxicity. We describe a case of a 54-year-old lady who presented with Takotsubo cardiomyopathy (TTS). This is the first case described where cardiac magnetic resonance imaging (CMR) was performed in the acute setting to help guide management.

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Timeline

Day 0	First bolus and infusion of FOLFOX chemotherapy regime administered
Day 1	Presentation to emergency department with chest pain and cardiogenic shock
Day 2–3	Good response to noradrenaline and dopamine inotropic support and a few hours of continuous positive airway pressure ventilatory support in intensive care unit
Day 4	Step-down to coronary care unit for further monitoring and titration of bisoprolol and perindopril. Patient was offered but declines coronary angiography due to anxiety surrounding the procedure. Cardiac magnetic resonance imaging (CMR) confirms Takotsubo cardiomyopathy and therefore angiography was not pursued further
6 weeks following discharge	CMR confirms full resolution of cardiomyopathy with normal biventricular function and no evidence of scarring

Case presentation

A 54-year-old lady presented to our emergency department because of left-sided burning chest pain radiating to the throat and left arm that had been present for several hours. This was associated with palpitations, nausea, and vomiting. Four months earlier, a sigmoid adenocarcinoma had been diagnosed with a solitary liver metastasis. She had undergone laparoscopic anterior resection and had started the first cycle of FOLFOX adjuvant chemotherapy (oxaliplatin, calcium folinate, and fluorouracil) as a bolus and as a continuous intravenous infusion, completed 1 day prior to the onset of the acute chest pain. She had a past history of a pituitary adenoma with transphenoidal surgery for which she was taking long-term hormone replacement as well as duodentitis and hypercholesterolaemia. She was hypotensive and tachycardic, with bilateral crepitations to the midzones of her lungs and jugular venous pressure was raised. Arterial blood gases were consistent with Type 1 respiratory failure. Electrocardiogram (ECG) confirmed sinus tachycardia with T-wave inversion in V4–6, I, and aVL. Bloods testing showed a raised troponin-I of 679 ng/L (high-sensitivity assay), white cell count of 11.4×10^9/L and C-reactive protein (CRP) of 5 mg/L. A bedside echocardiogram showed severe global impairment of left ventricular (LV) function (estimated ejection fraction 10–15%) and mild functional mitral regurgitation. She was initially managed with dual antiplatelets on the assumption that there was an underlying primary coronary cause to her presentation. She was transferred to our intensive care unit where intravenous noradrenaline and dopamine and high flow oxygen and was started. A brief period on continuous positive airway pressure was required. She responded to inotropic support and was stepped-down to our coronary care unit on Day 4 of the admission. Due to resolution of chest pain, lack of ECG evidence of evolving ischaemia and being unable to lie flat for the procedure for which she would require intubation and ventilation, a coronary angiogram was not performed emergently and was deferred for when she was more clinically stable. This was offered on Day 4 but the patient declined this due to anxiety surrounding the procedure. A cardiac magnetic resonance (CMR) scan scheduled on the same day showed good contraction of the basal segments of the left ventricle but was hypokinetic from the mid ventricle to the apex (i.e. in a non-coronary distribution). Overall, LV function was moderately impaired. Right ventricular (RV) size and function were normal. T1 and T2 mapping sequences confirmed LV oedema from the mid ventricle to the apex with relative sparing at the base. Contrast (late gadolinium enhancement, LGE) imaging, showed no evidence of myocardial scar or infarction (*Figures 1–3*) (Supplementary material). The CMR scan diagnosed TTS secondary

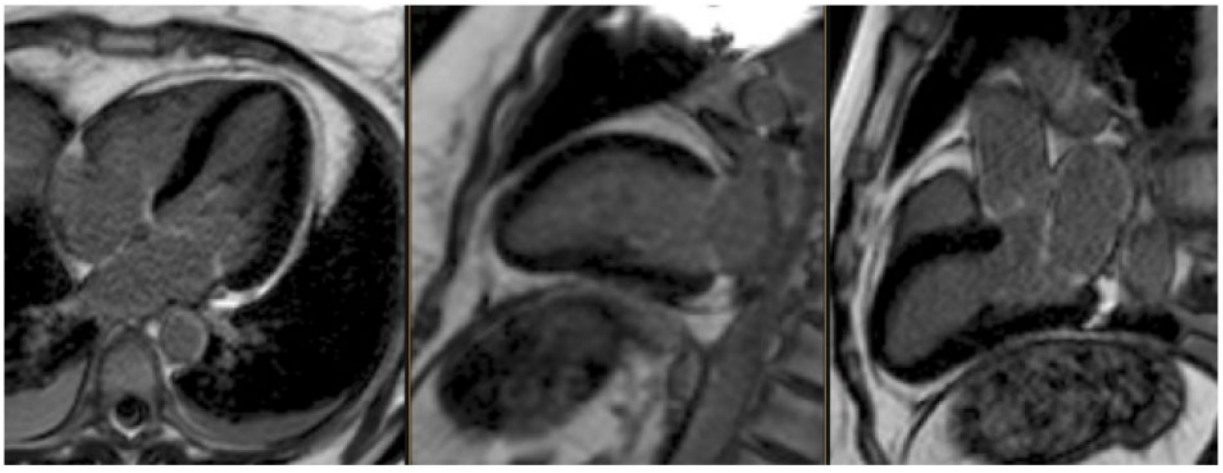

Figure 1 Cardiac magnetic resonance imaging on Day 4 of admission—four-chamber, vertical long-axis, and left ventricular outflow tract views.

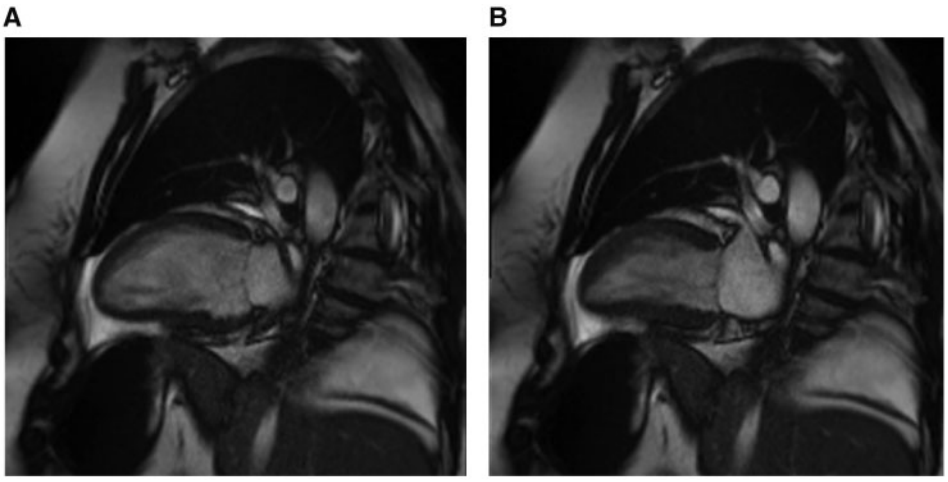

Figure 2 Cardiac magnetic resonance imaging on Day 4 of admission—two-chamber axis views in end-diastole (*A*) and end-systole (*B*) showing good basal contraction and hypokinetic mid-apical left ventricle.

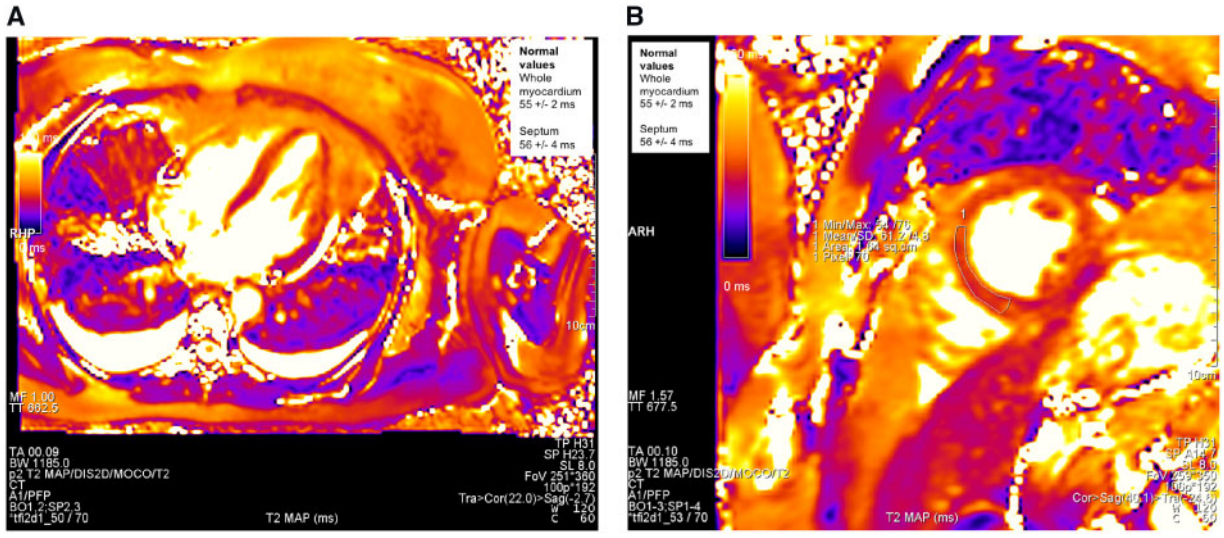

Figure 3 Cardiac magnetic resonance T2 mapping four-chamber (*A*) and short-axis (*B*) views showing global left ventricular oedema and inflammation which is worse in the mid-left ventricle.

to fluorouracil chemotherapy and the patient was discharged with perindopril and bisoprolol. In light of the Takotsubo pattern of features on her CMR, coronary angiography was not necessary. Follow-up CMR scan 6 weeks later confirmed resolution of the acute findings: no myocardial oedema with normal T1 and T2 tissue values, normal biventricular function, and no myocardial infarction (MI).

Discussion

This case report is an example of an acute cardiomyopathy secondary to fluorouracil chemotherapy and is the first case report that demonstrates how CMR was used to characterize the acute stress cardiomyopathy associated with this condition.

Fluorouracil chemotherapy is NICE guidance first-line adjuvant chemotherapy used to treat metastatic colorectal cancer. It includes fluorouracil, the anti-metabolite implicated in the cardiotoxicity of FOLFOX.

The mechanisms behind its cardiotoxicity are incompletely understood, however, coronary vasospasm, endothelial injury, and myocardial ischaemia have been proposed.[1–6] Clinical manifestations include coronary vasospasm, cardiomyopathy, pericarditis, and malignant arrhythmia resulting in cardiac arrest.[7–9]

Table 1 A table to summarize the previous published cases of stress cardiomyopathy associated with fluorouracil chemotherapy[10–14]

Authors	Demographics	Symptoms	Timing of 5-FU	Past cardiac history	ECG changes	Cardiac enzymes	Echo	Angiography findings	Presence of cardiogenic shock	Management	Prognosis
Sundravel *et al.*[10]	61-year-old woman	Shortness of breath and diaphoresis	Day 5	Paroxysmal atrial flutter—treated with ablation	SR and inferolateral ST changes	Positive	EF 25–30% hyperdynamic basal region, apical stunning	Normal	Yes	Impella CP assist device, respiratory support + diuretics, vasopressors, intubated and ventilated, 3 days, discharged Day 7	Improvement of LV ejection fraction to 35%, 3 days after initial echo
Basselin *et al.*[11]	48-year-old man	Chest pain	Day 2 (after 24 h)	No cardiac history	Abnormal'	Mildly positive	EF 15%—apical and median segment hypokinesis	No significant coronary lesions	Yes	Intra-aortic balloon pump, vasopressors	Recovery to normal ejection fraction a few days after initial echo
Cerny *et al.*[12]	57-year-old man	Chest pain	Day 1 (within 24 h)	No cardiac history	SR and ST depression v1+v2, subtle inferior ST elevation	Negative	EF 20%	No flow-limiting coronary stenosis	No	ACE inhibitors, calcium channel blocks	Rechallenged with 5-FU and CCBs, uneventful, full recovery of ejection fraction
Paiva *et al.*[13]	55-year-old woman	Chest pain	Day 1 (7 h)	No cardiac history, COPD, and limb thrombosis	SR and STE in I, II, aVL, V5, V6	Positive	Global left ventricular hypokinesis, more pronounced on the inferior, posterior and lateral walls, moderate MR	Normal coronary arteries	No	5-FU stopped, chest pain resolved with GTN, also treated with beta-blocker, aspirin, and clopidogrel	Switched to TOMOX—raltitrexate + oxaliplatin, patient died 7 months after initial diagnosis. Normal echo 2 months after occurrence
Iskander *et al.*[14]	33-year-old man	Myalgia, arthralgia, and shortness of breath	Day 3	No cardiac history	SR + TWI in V4–V6, followed by STE in V4–V6, I, aVL	Positive	EF 26%, non-dilated left ventricle	Normal coronary arteries		Beta-blocker, ACE inhibitor, MRA + dual antiplatelets	Repeat echo + CMRI 4 weeks after presentation—EF61% + structurally normal heart

5-FU, fluorouracil; ACE angiotensin converting enzyme; CCB, calcium channel blocker; CMRI, cardiac MRI; COPD, chronic obstructive pulmonary disease; EF, ejection fraction; GTN, glyceryl trinitrate; LV, left ventricle; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; SR, sinus rhythm; STE, ST elevation; TWI, T-wave inversion.

Five recent cases of LV dysfunction associated with fluorouracil chemotherapy have been described on PubMed literature search with salient features outlined in *Table 1*. The patients all had acutely severe impairment of LV function with no significant past cardiac history (except for one patient with paroxysmal atrial flutter with previous ablation). Patients were between 33 and 61 years of age with an almost even proportion of male to female (three were male). As with our patient, most patients developed symptoms early into their fluorouracil regimes (7–120 h). Chest pain was a feature in only 60% of cases, with shortness of breath and other non-specific symptoms being the predominant presenting complaint. Electrocardiogram findings were similarly heterogeneous. Troponin was negative in one patient. (Troponin was negative in 10% of patients with stress cardiomyopathy in a recent study.)[15]

All patients had normal coronary arteries. Two patients needed invasive circulatory support for cardiogenic shock (one with IMPELLA and one with intra-aortic balloon pump). Encouragingly as with our patient, all patients had complete resolution of LV dysfunction even despite critical illness. Fluorouracil chemotherapy was discontinued in three patients; however, it was reattempted in two patients, one of which tolerated this well, the other developed cardiac arrest after a third cycle but survived resuscitation. This matches previous evidence where fluorouracil cardiotoxicity has been shown to carry a high rate of recurrence with 20–100% incidence and a 40-fold higher risk of death following re-exposure to fluorouracic. Our patient was discontinued on FOLFOX and was switched to a Ralitritrexed based chemotherapy regime in accordance with current NICE guidance.[2] All patients had at least a beta-blocker or ACE inhibitor in-keeping with the management of LV systolic dysfunction (LVSD). In contrast, one patient had a calcium channel blocker (often not used in the presence of heart failure) perhaps reflecting the belief of an underlying vasospastic pathology in the development of the disease.[10–14,16]

The cardiac magnetic resonance imaging pattern of our patient's LV impairment is the classical picture of TTS. Other types of regional wall motion abnormality (RWMA) have been described to include mid-ventricular, basal, and regional ballooning but are much rarer occurring with incidences of 4–40%, 1–3%, and 1.5–7%.[17]

CMR in acute stress cardiomyopathy provides accurate visualization of RWMA, quantification of LV and RV function, and tissue characterization of myocardial oedema and areas of scar/fibrosis, thereby differentiating this from the phenotypically similar acute MI and myocarditis. In our patient, we find the classical features of TTS being an apical ballooning with apical and mid-ventricular systolic dysfunction. We found her RV function to be impaired during her bedside echo in Day 1 of admission but not in her CMR on Day 6 of admission. This is important as RV dysfunction has been associated with a more severe and prolonged course of TTS. The absence of LGE, a method of detecting myocardial fibrosis, is a significant feature as its presence associated with a poorer prognosis in cardiomyopathy. Diagnostic criteria for TTS also include RWMA in a non-coronary territory, early gadolinium uptake, and severe LVSD. Clinically, myocarditis in this case was considered as a differential diagnosis although thought to be less likely due to a CRP that was not significantly elevated. The CMR findings of TTS include a uniform transmural oedema as opposed to the findings of myocarditis which prefers the subepicardial and inferolateral regions. Lack of evidence of myocyte injury or scar caused by myocardial inflammation on LGE also made a diagnosis of acute myocarditis less likely. Furthermore, the use of CMR in the acute setting avoided risks of coronary angiography in our patient.[15,18]

Conclusion

Our case report is the first shown to describe the acute CMR features of fluorouracil-associated TTS; a complication with heterogeneous clinical features. CMR proved to be useful to diagnose TTS and exclude other important diagnoses of myocarditis and acute MI.

In this case, CMR scanning confirmed the acute diagnosis. The importance of the cardiotoxicity of chemotherapy is becoming increasingly recognized and is of interest to physicians as a differential diagnosis.

Lead author biography

Dr George Joy, MBBS MRCP, graduated from Kings College London Medical School with distinction in clinical practice in 2013. He is currently a cardiology trainee in South London Deanery and his clinical and research interests include interventional cardiology, cardiac MRI in cardiomyopathy and rare causes of myocardial infarction.

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 author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

References

1. Cassidy J, Bissett D, Spence R, Payne M. *Oxford Handbook of Oncology*, 4th ed. Oxford: Oxford University Press; 2015.
2. NICE 2018 Colorectal cancer: diagnosis and management, NICE clinical guideline 2011. https://www.nice.org.uk/guidance/cg131 (31 August 2019).
3. Südhoff T, Enderle MD, Pahlke M, Petz C, Teschendorf C, Graeven U, Schmiegel W. 5-Fluorouracil induces arterial vasocontractions. *Ann Oncol* 2004;**15**:661–664.
4. Jensen SA, Sorensen JB. 5-Fluorouracil-based therapy induces endovascular injury having potential significance to development of clinically overt cardiotoxicity. *Cancer Chemother Pharmacol* 2012;**69**:57–64.
5. Jensen SA, Hasbak P, Mortensen J, Sørensen JB. Fluorouracil induces myocardial ischemia with increases of plasma brain natriuretic peptide and lactic acid but without dysfunction of left ventricle. *J Clin Oncol* 2010;**28**:5280–5286.
6. Lestuzzi C, Vaccher E, Talamini R, Lleshi A, Meneguzzo N, Viel E, Scalone S, Tartuferi L, Buonadonna A, Ejiofor L, Schmoll H-J. Effort myocardial ischemia during chemotherapy with 5-fluorouracil: an underestimated risk. *Ann Oncol* 2014;**25**:1059–1064.
7. Ray JC, Cho P, Dragon M, Graham CG. A case of 5-fluorouracil-induced cardiac arrest. *J Emerg Med* 2016;**50**:e1–e6.

8. Maréchal S, Racaru V, Houbiers G, Graas MP. Le cas clinique du mois Péricardite après administration de 5-fluorouracil. *Rev Med Liege* 2015;**70**:360–366.
9. Kim SM, Kwak CH, Lee B, Kim SB, Sir JJ, Cho WH, Choi SK. A case of severe coronary spasm associated with 5-fluorouracil chemotherapy. *Korean J Intern Med* 2012;**27**:342–345.
10. Sundravel S, Alrifai A, Kaback M, Ghumman W. FOLFOX induced takotsubo cardiomyopathy treated with Impella assist device. *Case Rep Cardiol* 2017;**2017**:8507096.
11. Basselin C, Fontages T, Descotes J, Chevalier P, Bui-Xuan B, Feinard G. 5-Fluorouracil-induced Tako-Tsubo-like syndrome. *Pharmacotherapy* 2011;**31**:226.
12. Cerny J, Hassan A, Smith C, Piperdi B. Coronary vasospasm with myocardial stunning in a patient with colon cancer receiving adjuvant chemotherapy with FOLFOX regimen. *Clin Colorectal Cancer* 2009;**8**:55–59.
13. Paiva CE, Paiva BSR, Garita R, Michelin OC, Okoshi K. Acute coronary syndrome associated with continuous 5-Fluorouracil infusion in a patient with metastatic colorectal cancer-a case report with a discussion on this clinical dilemma. *J Gastrointest Cancer* 2009;**40**:133–137.
14. Iskander MZ, Quasem W, El-Omar M. 5-Fluorouracil cardiotoxicity: reversible left ventricular systolic dysfunction with early detection. *BMJ Case Rep* 2015;doi: 10.1136/bcr-2015-209347.
15. Eitel E, Knobelsdorff-Brenkenhoff FV, Bernhardt P, Carbone I, Muellerleile K, Aldrovandi A. Clinical characteristics and cardiovascular magnetic resonance findings in stress (Takotsubo) cardiomyopathy. *JAMA* 2011;**306**:277–286.
16. Ransom D, Wilson K, Fournier M, Simes RJ, Gebski V, Yip D, Tebbutt N, Karapetis CS, Ferry D, Gordon S, Price TJ. Final results of Australasian Gastrointestinal Trials Group ARCTIC study: an audit of raltitrexed for patients with cardiac toxicity induced by fluoropyrimidines. *Ann Oncol* 2014;**25**:117–121.
17. Kato K, Lyon AR, Ghadri JR, Templin C. Takotsubo syndrome: aetiology, presentation and treatment. *Heart* 2017;**103**:1461–1469.
18. Kuruvilla S, Adenaw N, Katwal AB, Lipinski MJ, Kramer CM, Salerno M. Late gadolinium enhancement on cardiac magnetic resonance predicts adverse cardiovascular outcomes in non-ischaemic cardiomyopathy. *Circ Cardiovasc Imaging* 2014;**7**:250–258.