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.
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 $11.4 \times 10^9/L$ and C-reactive protein (CRP) of $5 \text{mg/L}$. 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...
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. Clinical manifestations include coronary vasospasm, cardiomyopathy, pericarditis, and malignant arrhythmia resulting in cardiac arrest.
| Authors     | Demographics | Symptoms | Timing of S-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 blockers | 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—ralitretinaxe + 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, Positive 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 |

S-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.)

All patients had normal coronary arteries. Two patients needed invasive circulatory support for cardiogenic shock (one with IMPPELLA 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 fluorouracil. Our patient was discontinued on FOLFOX and was switched to a Ralitritrexed based chemotherapy regime in accordance with current NICE guidance. 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.

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%, respectively.

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.

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.

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.

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