CASE REPORT

5-Fluorouracil-induced acute reversible heart failure not explained by coronary spasms, myocarditis or takotsubo: lessons from MRI

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SUMMARY

A 69-year-old woman presented with arterial hypotension, pulmonary oedema and a severely depressed left ventricular ejection fraction (LVEF) of 25% only 3 days after having received her first treatment for colorectal cancer with 5-fluorouracil (5-FU)-based therapy. The ECG demonstrated widespread ST-segment depression and echocardiography showed uniform hypokinesia of all left ventricular (LV) myocardial segments without signs of regional LV ballooning. Coronary angiography was normal and the patient gained full recovery after receiving treatment with heart failure medication. Interestingly, cardiac MRI scan 9 days later showed a normal LVEF with signs of neither myocardial oedema nor necrosis. Despite the high therapeutic efficacy of 5-FU in treatment of colorectal cancer, it is associated with undesired cardiac toxicities including coronary spasms, toxic inflammation and takotsubo cardiomyopathy. However, our patient did not fulfil the diagnostic criteria for the aforementioned complications. Based on this case report, we discuss alternative mechanisms including myocardial adenosine triphosphate depletion suggested from animal experiments.

BACKGROUND

Therapy with 5-fluorouracil (5-FU) and its prodrug capecitabine is widely used in the treatment of solid neoplasms, notably breast, pancreas, colorectal, and head and neck cancer. Common adverse effects of 5-FU include diarrhoea, mucositis and myelosuppression. Cardiac toxicity is less often described, and knowledge about it is incomplete.¹ Cardiac toxicity often relates to angina, with transient myocardial ischaemia and necrosis, which is explained by coronary spasms.² Thus, while patients with 5-FU-induced chest pain are considered as candidates for coronary angiography, this is often normal and transient ST elevations are suggested to be due to the vasospasms that are seen on angiography.^{3–5} Cardiogenic shock and sudden death are seen,¹ which, if not explained by coronary spasms, can sometimes be attributed to toxic myocardial inflammation or stress cardiomyopathy (takotsubo) with localised myocardial function depression, often with apical and/or mid-ventricular ballooning. Acute systolic heart failure (HF) due to 5-FU is rare if not related to myocardial infarction, with widespread coronary spasms, toxic myocarditis or takotsubo cardiomyopathy. To spur further research into cardiac 5-FU toxicity, it is important

to acknowledge the full range of clinical presentations. In this case report, we describe a patient undergoing 5-FU therapy who had transient acute severe LV systolic failure unrelated to coronary spasms, toxic myocarditis or stress cardiomyopathy (takotsubo). Also, we discuss possible alternative mechanisms that may explain this rare find.

CASE PRESENTATION

A 69-year-old woman with no prior history and no earlier symptoms of ischaemic heart disease, presented with acute onset of dyspnoea only 3 days after having received her first injection with 5-FU aimed to treat colorectal cancer. The patient was given leucovorin, oxaliplatin (85 mg/m² administered as an intravenous bolus) and a total of 400 mg/m² of 5-FU administered as an intravenous bolus followed by 2400 mg/m² of 5-FU as a continuous intravenous infusion for 46 hours. The patient presented with sinus-tachycardia and paroxysms of atrial fibrillation with abnormal ECG signs including anterolateral ST-segment depression and T wave inversions (I, aVL and V₂–V₆) (figure 1). The patient was preshocked with an arterial blood pressure of 92/59 mm Hg and an arterial saturation of 88%, whereas arterial pH and carbon dioxide tension were within normal limits. On auscultation, the patient had bilateral rales but no cardiac murmurs.

INVESTIGATIONS

On chest X-ray, signs of pulmonary oedema were present (figure 2). Acute blood tests demonstrated elevated troponin, creatine kinase-MB and D-dimer of 2540 ng/L (normal <49 ng/L), 12 µg/L (normal <4 µg/L) and 6.2 FEU/L (normal <0.5 FEU/L), respectively. Similarly, no signs of infection were present and all values (temperature, S-leucocytes and C reactive protein) were found to be normal. However, elevated D-dimer (alongside with thrombocytosis and hyperfibrinogenaemia) in patients with cancer is a sign of a hypercoagulable state; nevertheless, due to dyspnoea, tachycardia and elevated D-dimer, an acute high-resolution CT scan was ordered to rule out pulmonary embolism, which confirmed findings of pulmonary oedema. Subsequently, acute transthoracic echocardiography (TTE) was ordered to assess cardiac function. The TTE demonstrated a non-dilated LV (LV end-diastolic diameter of 50 mm) with a universally depressed systolic LV function and a LV ejection fraction of

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Figure 1 Above, ECG at baseline; below, ECG at admission.

25% (normal >55%). There were no signs of localised myocardial dysfunction, as all segments of the LV were uniformly hypokinetic. Right ventricular function was (near-normal) normal with a tricuspid annular plane systolic excursion of 18 mm (normal >18 mm). Also, there were no signs of valve disease or pericardial effusion.

DIFFERENTIAL DIAGNOSIS

Based on the echocardiography and chest X-ray findings, a diagnosis of pulmonary oedema secondary to severe acute LV systolic dysfunction was made. In addition, infection and pulmonary embolism were excluded as competing causes by performing a CT scan and blood tests. Notably, prior to 5-FU

Figure 2 Biplane chest X-ray showing signs of pulmonary oedema with pleural effusion.

Figure 3 T2-weighted MRI (short axis, three levels) of the left ventricular (LV) (short tau inversion recovery sequences; diastole). Please note the uniformly enhancing LV myocardium, that is, without signs of localised myocardial oedema.

treatment, the patient had been known to have normal cardiac function.

TREATMENT

Suspecting cardiac toxicity from 5-FU, the latter was discontinued, and the patient was treated with intravenous diuretics and nitroglycerine. On this regimen, her pulmonary oedema quickly resolved and arterial blood pressure normalised. Subsequently, she was treated with systolic heart failure medications including an ACE-inhibitor, a β -blocker and spironolactone.

OUTCOME AND FOLLOW-UP

A coronary angiography performed on day 3 was without signs of coronary sclerosis, thrombosis or spasms. Nine days after having presented with acute severe pulmonary oedema and severe LV systolic dysfunction, the ECG and cardiac biomarkers had normalised, and a MRI cardiac MR (CMR) study demonstrated a normal LV without dilation and with a LV ejection fraction of 60%. In line with that, peak-ejection and peak-filling rates were also normal. There were no signs of localised myocardial thinning nor of hypo-akinesia or akinesia. Additionally, there were no signs of localised LV myocardial oedema on T2-weighted images (short tau-inversion recovery sequences) nor of localised hyperenhancement on late gadolinium images (late gadolinium enhancement (LGE); inversion recovery sequences performed 10 min after

intravenous injection of gadolinium 0.1 mmol/kg of gadobutrol following appropriate inversion time selection guided by a look-locker pulse sequence; figures 3–5). Ultimately, the patient continued on HF medications, restarted chemotherapy with oxaliplatin and irinotecan, and is now fully recovered.

DISCUSSION

The cardiotoxic potential of 5-FU is well recognised by oncologists and cardiologists alike, but the mechanism(s) responsible is not well elucidated. Our case report suggests that, in some cases, alternative mechanisms than those conventionally suggested may be at play.

A coronary artery spasm is often suspected but, as illustrated in our case, a normal coronary angiography without signs of spasms, absence of ST elevations in the ECG and, additionally, a normal CMR, demonstrated that this was not the obvious reason for the uniformly depressed LV systolic function. Coronary spasms usually present with ST-segment elevation¹ and would have been associated with myocardial depression in myocardial segments supplied by the coronary artery in question. Also, spasms would often be noted on the coronary angiography, but this was not the case in our patient. Further, widespread coronary spasms on CMR would have been associated with myocardial oedema⁶ and LGE hyperenhancement (necrosis) in a subendocardial pattern.^{7 8}

Figure 4 Two-chamber left ventricular MRI late gadolinium enhancement image.

In some cases, takotsubo (TS) or 'stress' cardiomyopathy may be suspected,^{3–5 9–16} and it may be that our patient suffered from a variant of TS. However, patients with TS present with localised myocardial depression most often including the apical and mid-ventricular segments, and with ST-segment elevations. Furthermore, based on Mayo Clinic criteria,¹⁷ in the largest study on TS to date,¹⁸ 96% of patients presented with apical or mid-ventricular ballooning. The Gothenburg criteria¹⁹ specifically exclude TS diagnosis if toxicity from a drug is implicated. However, LV systolic dysfunction with LV dilation not conforming to localised segments of the LV can be seen in patients with sepsis, especially if treated with catecholamines, but this was not the case in our patient.

Other mechanisms implicated in reviews include direct myocardial²⁰ and endothelial damage,²¹ thrombogenicity²² and toxic myocarditis.^{23 24} These mechanisms, however, would have readily been diagnosed by LGE CMR since they would also have been associated with myocardial oedema and signs of LGE hyperenhancement relating to myocardial inflammation and necrosis.²³

The few previous case reports of 5-FU/capecitabine-induced acute LV systolic dysfunction are with ST-segment elevation in the ECG and have been related to coronary spasm.^{4 13–15 25} Some of these case reports undoubtedly do relate to widespread coronary spasm, but we speculate that a number of previously reported 5-FU cases may be related to other mechanisms. For example, a potential mechanism has been suggested from animal models in which 5-FU have been shown to deplete myocardial high-energy phosphates, in particular, adenosine triphosphate (ATP).^{20 26–28} With depletion of ATP levels, severe diastolic and systolic impairment is seen, especially in the LV, the cardiac ventricle serving the high-pressure circulation. Also, it is expected that LV systolic as well as diastolic function will recuperate as soon as 5-FU is discontinued and the patient is placed on HF medications known to lower myocardial ATP requirements. Indeed, to ascertain that our patient suffered from ATP depletion, it would have required myocardial ³¹P-phosphate MR spectroscopy in the acute phase, but we find it intriguing that

Figure 5 Short axis left ventricular MRI late gadolinium enhancement image.

she did demonstrate findings that were fully in line with a mechanism implicating lowered energy supply (uniformly depressed cardiac function, quick recovery and no findings on CMR implicating well-known mechanisms). In a recently published review, myocardial ATP depletion was implicated as the cause of reversible tachycardia-induced cardiomyopathies,²⁹ and the 'engine out of fuel' hypothesis was proposed for lowered ATP generation in a number of cardiomyopathies.³⁰ It is interesting that, despite animal experiments demonstrating myocardial ATP-depletion with 5-FU, this mechanism is rarely discussed in the literature on 5-FU cardiotoxicity.

In conclusion, we have reported a case of 5-FU-induced severe systolic LV dysfunction and ECG findings suggestive of ischaemia, but without any sign of myocardial infarction, coronary stenosis, coronary spasms, stress cardiomyopathy or toxic myocarditis on echocardiography, coronary angiography or MRI. Despite the high therapeutic efficacy of 5-FU in treatment of colorectal cancer, it is associated with undesired cardiac

Learning points

- ▶ Cardiotoxic side effects of 5-fluorouracil (5-FU)/capecitabine often include coronary spasm, but may include severe systolic heart failure from other causes.
- ▶ 5-FU/capecitabine must be paused until the cause of the symptoms is diagnosed, and if 5-FU toxicity is suspected, it should be discontinued.
- ▶ Heart failure medication should be initiated immediately.
- ▶ In the acute phase, echocardiography is necessary; subsequently, cardiovascular MRI including imaging of myocardial oedema (with T2-weighted sequences) and fibrosis (with gadolinium contrast studies) should be considered.
- ▶ Mechanisms other than coronary spasms or stress cardiomyopathy might play a role in the course of 5-FU cardiotoxicity, but further research is clearly needed.

toxicities. Physicians and researchers must be aware of the full spectrum of patients' clinical presentations with 5-FU cardiotoxicity. Accordingly, animal experiments suggest myocardial ATP depletion to be implicated, and case reports such as ours suggest that conventional mechanisms used to explain 5-FU toxicity may not always be applied.

Competing interests None declared.

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