CASE REPORT

5-Fluorouracil cardiotoxicity: reversible left ventricular systolic dysfunction with early detection

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SUMMARY

A 33-year-old man presented to hospital with acute shortness of breath and evolving ST segment changes on ECG 3 days following a cycle of 5-fluorouracil (5-FU) for colon cancer. Despite no cardiac history, subsequent echocardiogram showed severe left ventricular systolic dysfunction. The patient was initially treated with heart failure medications and his coronary angiogram was normal. Chemotherapy was stopped and he was started on nitrates and calcium channel blockers. A repeat echocardiogram and cardiac MRI a week later showed complete resolution of his left ventricular dysfunction and he was discharged home. This case report summarises 5-FU cardiotoxicity, and emphasises the importance of early recognition and correct treatment, as left ventricular systolic dysfunction in this context is potentially reversible.

of cardiotoxicity is vital as correct management will often lead to a good outcome.

CASE PRESENTATION

A 33-year-old man was admitted to hospital following a 1-day history of feeling generally unwell following chemotherapy. He described generalised myalgia, arthralgia and shortness of breath. He was being treated for bowel cancer and received 5-FU along with oxaliplatin 3 days prior to presentation. On arrival to hospital, he described a feeling of general malaise and shortness of breath. However, he did not report any chest pain. Fifteen years prior, he was also treated for an osteosarcoma for which he received cisplatin and doxorubicin combination chemotherapy. Cardiac MRI following chemotherapy at the time showed normal cardiac structure and function.

Initial ECG during this presentation showed lateral T wave inversion in V4–V6 (figure 1) with no other reciprocal changes. On clinical examination, he was haemodynamically stable, heart sounds were normal and chest was clear.

However after a few hours, the patient started to report of flu-like symptoms, myalgia and rigours. There was chest tightness as well as orthopnoea. A repeat ECG showed dynamic changes and T wave inversion in the lateral leads followed by ST elevation in V4–V6, I, aVL and the inferior leads (figure 2). Troponin I was raised at 109 ng/L. Echo demonstrated severely impaired left ventricular

BACKGROUND

Cardiotoxicity following chemotherapy is a rare but important side effect as it carries a great risk of morbidity and mortality if unrecognised.¹ 5-Fluorouracil (5-FU) is frequently used as a chemotherapy agent in gastrointestinal malignancies and cardiotoxicity secondary to this is a well-recognised complication although not often seen in daily clinical practice.² Clinical presentation in the emergency department often mimics acute coronary syndrome (ACS) or acute decompensation of heart failure. Recognition

Figure 1 Initial T wave inversion in V4–V6.

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Figure 2 Progressive ECG changes. ST elevation in V4–V6, I, aVL and inferior leads.

(LV) systolic dysfunction with an ejection fraction of 26% (figure 3). The left ventricle was not dilated and there was no pericardial effusion or valvular abnormalities. The patient was therefore treated with heart failure medications consisting of a β -blocker, ACE inhibitor and mineralocorticoid receptor antagonist as well as dual antiplatelet therapy.

Following this, an angiogram was arranged, which showed normal coronary arteries (figure 4). The patient was started on a calcium channel blocker and nitrates. Dual antiplatelet therapy was stopped. A repeat echocardiogram (figure 5) and cardiac MRI were also performed after a week, and showed complete resolution of LV systolic dysfunction with normal ejection fraction at 61% and a structurally normal heart. The patient improved and was subsequently discharged home.

INVESTIGATIONS

Initial echocardiogram showed severe LV systolic dysfunction with an ejection fraction of 26%. Repeat echocardiogram a week later showed complete resolution of this, with an ejection fraction of 61%.

TREATMENT

Assuming coronary arteries are normal, treatment is usually conservative, aimed at the underlying coronary vasospasm and resulting LV systolic dysfunction, which normally recovers. Success rates have been reported to be around 70–90%.² In the case of our patient, conventional treatment with heart failure

medications as well as calcium channel blockers and nitrates for vasospasm proved beneficial. On hindsight, it is difficult to determine with certainty whether the resulting systolic dysfunction would have resolved on its own with cessation of the chemotherapy agent.

Premedication with calcium channel blockers to prevent coronary vasospasm has not proven to be of benefit as demonstrated by Eskilsson and Albertsson,³ in which verapamil 120 mg three times a day was administered prophylactically. In addition to this, there has been no convincing clinical evidence of the use of any other agents prophylactically prior to 5-FU administration. Cessation of the drug or reduction in dose remains the most important step in the management of these patients.

OUTCOME AND FOLLOW-UP

The patient remains well from a cardiac point of view 6 months postadmission and is under continuous review by the oncology team.

DISCUSSION

5-Fluorouracil

5-FU is an antimetabolite from the fluoropyrimidine group and is increasingly popular as a chemotherapy agent in a combined chemotherapy regime for gastrointestinal cancers or as a neoadjuvant agent. Thymidylate synthase, a crucial enzyme in pyrimidine nucleotide synthesis, is inhibited, and this leads to inhibition of DNA synthesis and repair.⁴ Oncology outcomes are good, with reports of absolute risk reduction in 5-year mortality of 5.8% in resectable gastric cancers when combined with surgical resection as reported in a meta-analysis by Paoletti *et al.*⁵ As with all forms of chemotherapy, side effects such as mucositis, diarrhoea and immunosuppression are common. Cardiotoxicity is a much rarer event but is more serious due to the risk of ACS, cardiomyopathy and direct myocardial damage. Patients can also present with life-threatening arrhythmias.² At present, the rate of symptomatic cardiotoxicity from 5-FU treatment is reported to be around 1.2–4.3% and is more likely to occur with longer infusions compared with bolus injections.⁶ LV dysfunction is a relatively rare complication and a review by Saif and colleagues quoted an incidence of LV dysfunction of around 2%. They noted that the main presentations were of angina (45%), myocardial infarction (22%) and arrhythmias (23%).⁷

Figure 3 Initial echocardiogram showed severe left ventricular dysfunction with an ejection fraction of 26%.

Figure 4 Normal coronary arteries.

Mechanisms of toxicity

The exact mechanism of cardiotoxicity is unclear, but several theories have been postulated, primarily coronary vasospasm leading to acute ischaemia, direct toxic effect on the myocardium and a hypercoagulable state causing a thrombotic event.

Coronary vasospasm

The clinical presentation is often similar to ACS with patients reporting chest pain or tightness accompanied by a rise in troponin-I or other markers of myocardial damage. ECG changes are often ischaemic with ST segment changes. These investigations, however, do not always reflect coronary artery disease (CAD), as numerous case reports have described normal coronary arteries on angiography in these patients. Coupled with good response to nitrates and calcium channel blockers, as was the case in our patient, this strongly supports the theory of coronary vasospasm underlying the clinical presentation.

Thrombotic event

5-FU can also cause direct injury to endothelial cells. A sequelae of this would be platelet aggregation and, ultimately, thrombus formation. Despite not having previous CAD, a patient can potentially develop endothelial dysfunction and therefore experience a pathophysiological cascade of events that leads to thrombus formation.⁸ Further evidence has also been discovered that seems to support a prothrombotic state in these patients. Kuzel *et al* administered 5-FU in 10 patients with cancer and measured assays for protein C, protein S and fibrinopeptide A. There is a reduction in the level of protein C activity with coexisting increase in fibrinopeptide A in these patients, which

supports activation of coagulation.⁹ A combination of endothelial injury and a hypercoagulable state unsurprisingly creates a favourable environment for thrombus formation.

Direct toxic effect on the myocardium

Another possibility is a direct toxic effect on the myocardium. The current literature reports several different direct toxic effects. Among those that have been seen are haemorrhagic myocardial infarction, LV hypertrophy with necrosis and apoptosis of the endothelial cells, diffuse myocarditis and sarcoplasmic reticulum dilation.² These will more often than not give rise to a diffuse area of systolic dysfunction seen on echocardiography or functional imaging.

Learning points

- ▶ Acute shortness of breath and chest discomfort in a patient with ECG changes is not always due to obstructive coronary artery disease.
- ▶ Be aware of chemotherapy and other potential drugs that could potentially cause acute left ventricular failure, and a presentation mimicking acute coronary syndrome.
- ▶ Prompt cessation of chemotherapy drugs and conservative management with vasodilators are normally sufficient in these patients, as the underlying mechanism is usually severe coronary artery vasospasm.

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Figure 5 Repeat echocardiogram showed complete recovery of left ventricular systolic function.

Reminder of important clinical lesson

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