5-Fluorouracil cardiotoxicity

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5-FLUOROURACIL CARDIOTOXICITY

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ABSTRACT

The increasing prevalence of malignancies in the current population sees increasing usage of chemotherapy agents, which in itself carries various side effect profiles. We report a case of 5-fluorouracil (5-FU) cardiotoxicity in a young gentleman with no pre-existing cardiac history who was given his first ever dose of 5-FU. Mechanisms of 5-FU cardiotoxicity are varied, but most commonly involves an element of intense coronary vasospasm with accompanying transient global left ventricular systolic dysfunction (LVSD). Apart from cessation of 5-FU, treatment is mainly conservative and outcomes are good with potential reversibility of LVSD.

INTRODUCTION

Cardiotoxicity following chemotherapy is a rare but important side effect as it carries a great risk of morbidity and mortality if unrecognized.[CITATION Kha13 \l 1033] 5-fluorouracil (5FU) is frequently used as a chemotherapy agent in gastrointestinal malignancies and cardiotoxicity secondary to this is a well-recognized complication although not often seen in daily clinical practice.[CITATION Kha13 \l 1033] Clinical presentation in the Emergency Department often mimics acute coronary syndrome or acute decompensation of heart failure. Recognition of cardiotoxicity is vital as correct management will often lead to a good outcome. We report a case of 5-FU cardiotoxicity in a young gentleman who presented to our cardiology department via the primary percutaneous coronary intervention (PCI) pathway.

CASE REPORT

A 33 year-old man was admitted to hospital following a 1 day-history of feeling generally unwell following chemotherapy. He was being treated for bowel cancer which was diagnosed 2 months prior as a poorly differentiated mucinous signet ring tumour in his proximal descending colon. A staging CT scan staged the tumour as T4 N2 M0 and he had already undergone an extended right hemi-colectomy for the first part of his treatment. Following this, he commenced chemotherapy and received 5-fluorouracil (5FU) along with Oxaliplatin 3 days prior to presentation. This was administered as an infusion via a Hickman line and was his first exposure to 5-FU.

On arrival to hospital he described a feeling of general malaise, shortness of breath, and atypical chest pain. However, he did not report any chest pain. Fifteen years prior, he was also treated for a left tibial osteosarcoma for which he received Cisplatin and Doxorubicin combination chemotherapy along with tumour resection and prosthesis insertion. Cardiac MRI following chemotherapy at the time showed normal cardiac structure and left ventricular function.

Initial ECG during this presentation did not show any dynamic ischaemic changes. On clinical examination he was haemodynamically stable, heart sounds were normal and

chest was clear. Therefore the decision was made to not proceed to primary PCI at this point and treat him medically for acute coronary syndrome (ACS).

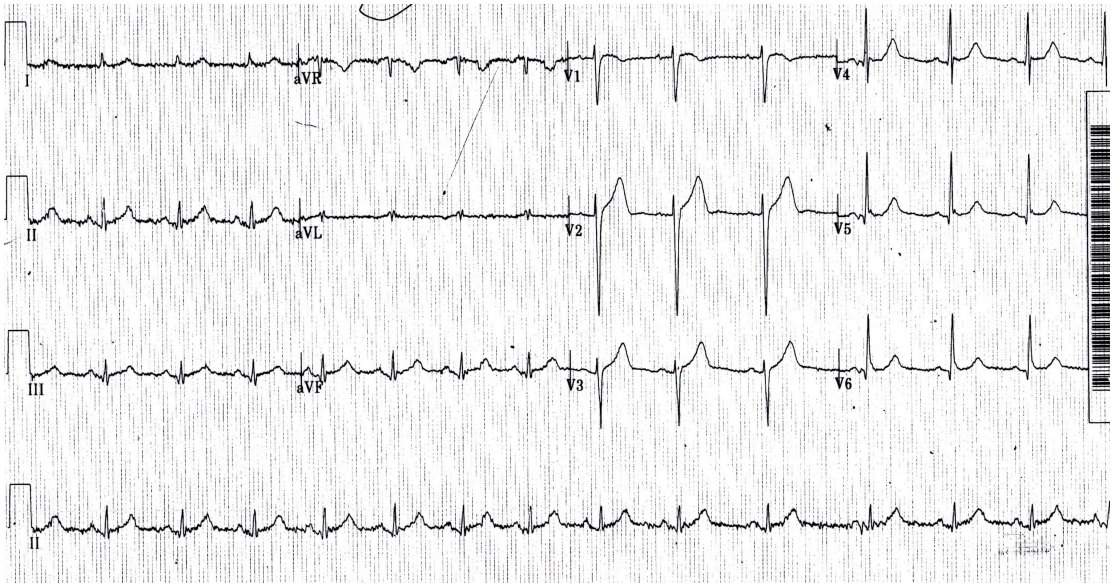


Figure 1 – Initial ECG on presentation.

However after a few hours, the patient started to complain of flu-like symptoms, myalgia, and rigors. There was chest tightness as well as orthopnoea but he was not pyrexial. A repeat ECG showed dynamic changes in the form of T wave inversion in leads V3 – V6 and also the inferior leads. Another ECG 10 minutes later demonstrated further changes in the form of saddle-shaped ST elevation in leads V4-V6. Troponin I 8 hours post admission was raised at 109 ng/L (normal lab values 1 – 14 ng/L). Echo demonstrated severely impaired left ventricular systolic dysfunction (LVSD) with an ejection fraction of 26%. The left ventricle was not dilated and there was no pericardial effusion or valvular abnormalities. The LVSD was global and there were no regional wall motion abnormalities (RWMA).

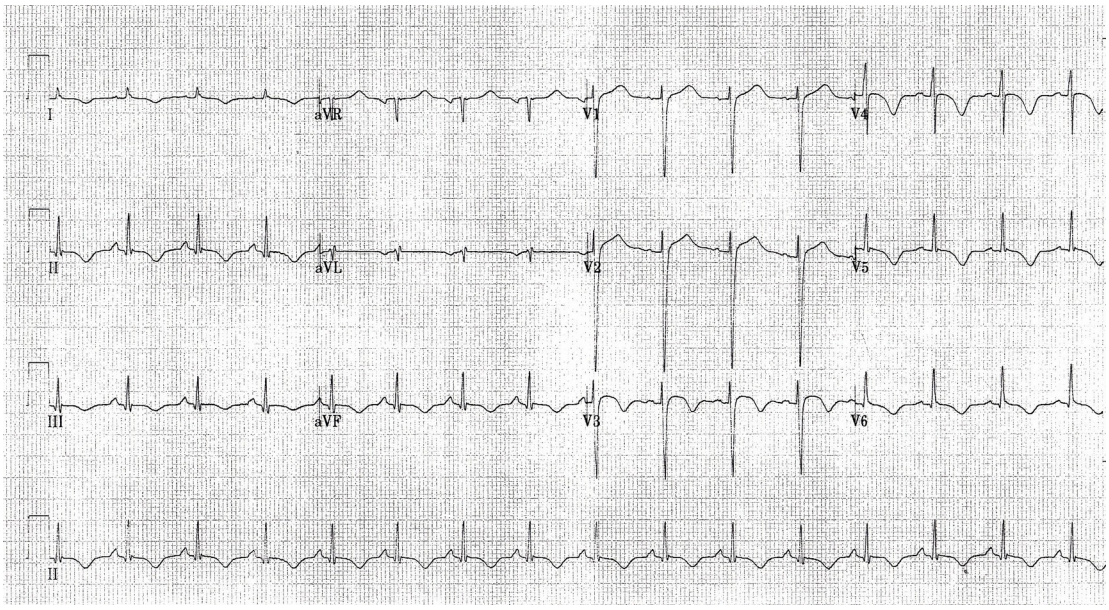


Figure 2 – Second ECG while patient was complaining of chest tightness. Note T wave changes in leads II, III, aVF as well as V3 – V6

As a result of his ECG changes, raised Troponin and clinical symptoms, the working diagnosis at this juncture was acute coronary syndrome (ACS) with a severely reduced ejection fraction. He was therefore treated with heart failure medications consisting of a beta-blocker (Bisoprolol 1.25 mg), ACE inhibitor (Ramipril 1.25 mg) and mineralocorticoid receptor antagonist (Spironolactone 25 mg) as well as dual antiplatelet therapy (Aspirin 75 mg and Clopidogrel 75 mg).

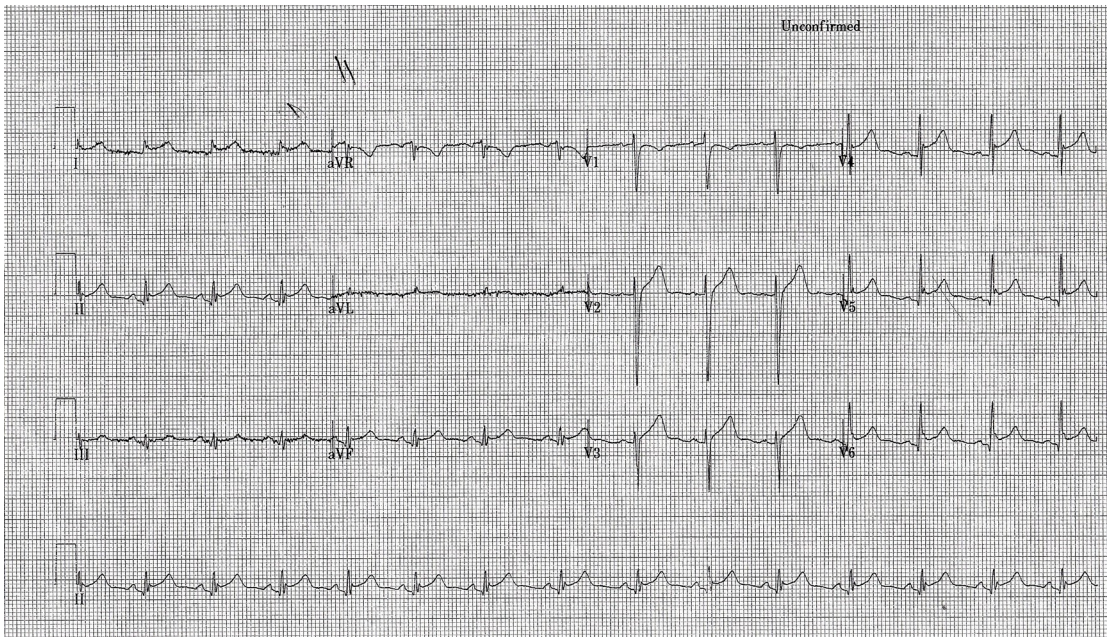


Figure 3 – A further ECG 10 minutes after the second ECG demonstrated saddle shaped ST elevation in leads V4 – V6

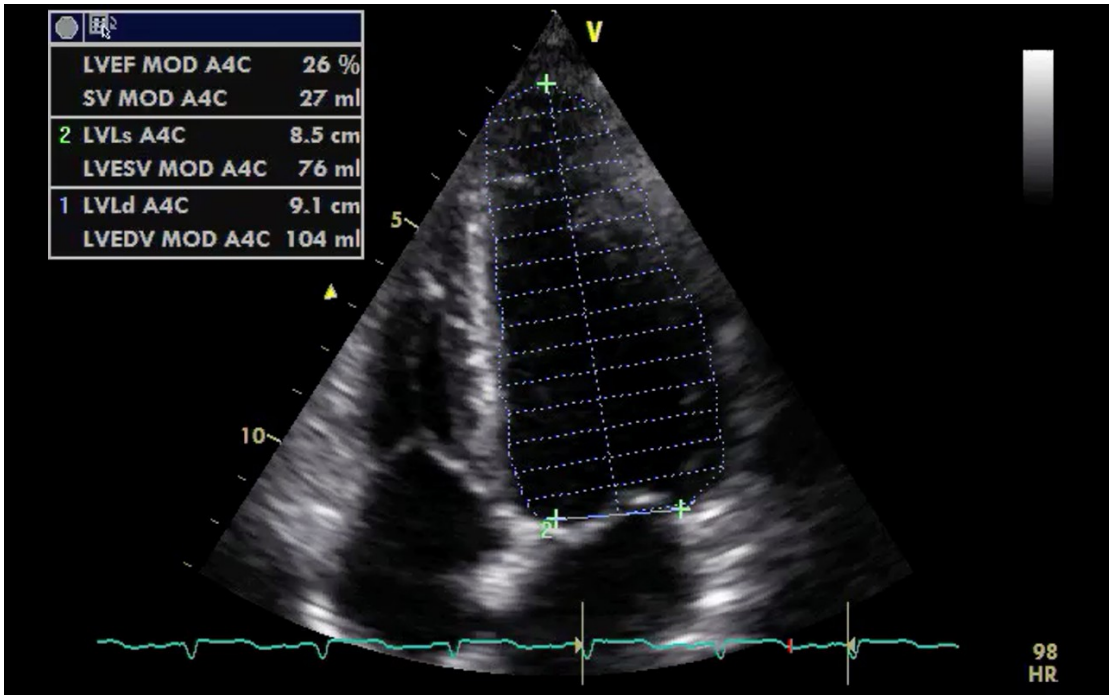
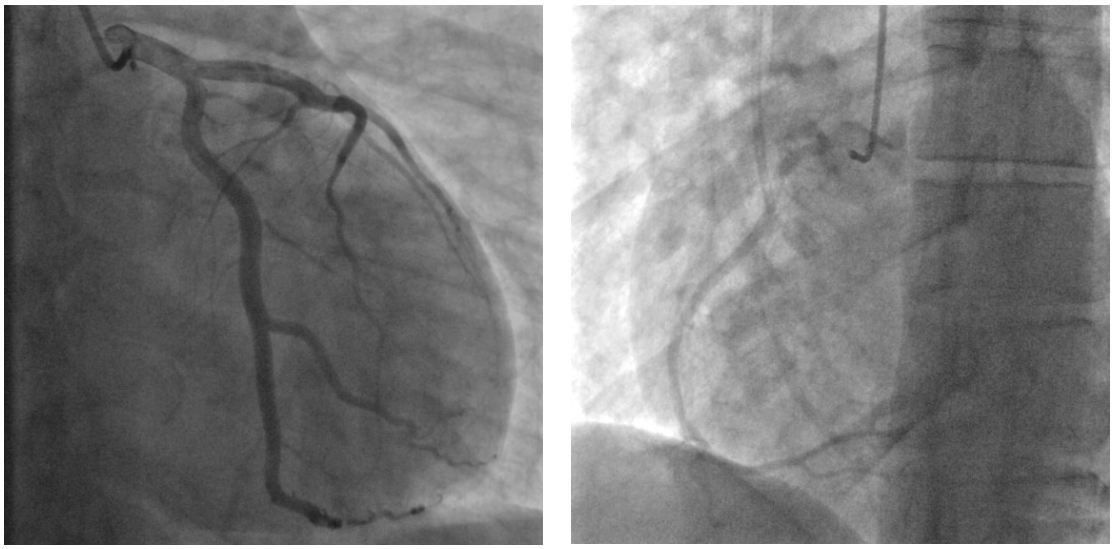


Figure 4 – Echo demonstrating a left ventricular ejection fraction (LVEF) of 26%. LVESV: Left ventricular end-systolic volume, LVEDV: Left ventricular end-diastolic volume, SV: systolic volume, MOD A4C: method of discs apical 4-chamber.

The following day, an angiogram was arranged which showed normal coronary arteries. All heart failure medications were stopped and he was commenced on a calcium channel blocker and nitrates. A repeat echocardiogram and cardiac MRI were also performed after a week and this showed a 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.



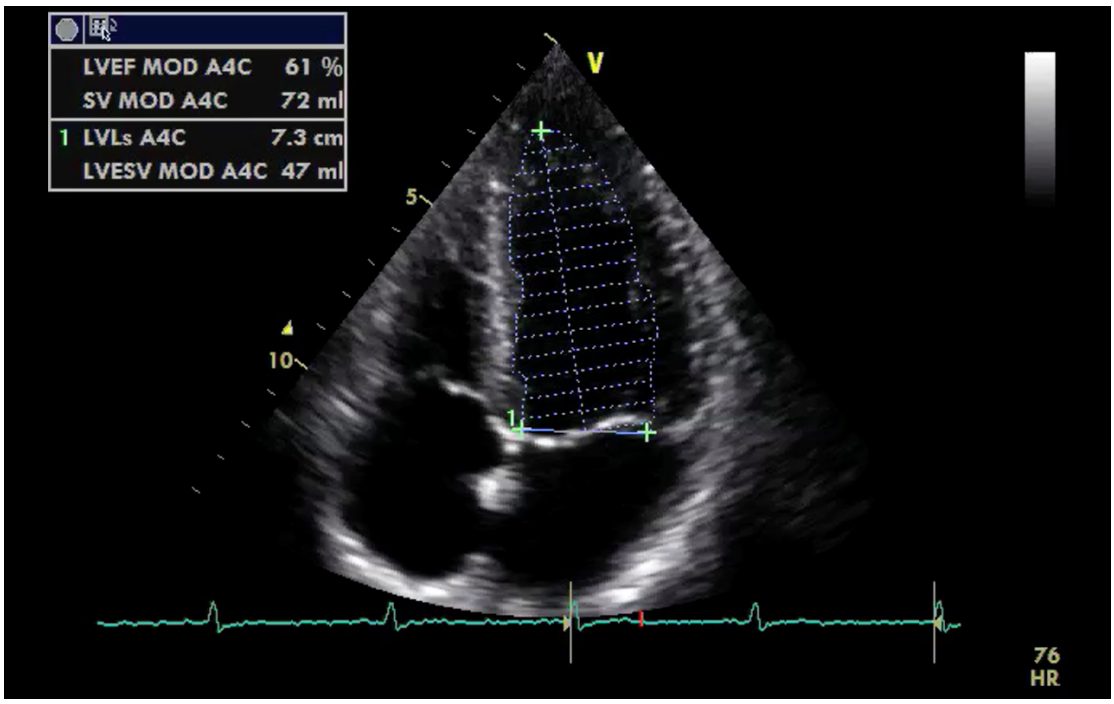


Figure 1

DISCUSSION

5-FU

5-fluorouracil is an anti-metabolite 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[CITATION Shr09 \l 1033]. 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[CITATION Pao10 \l 1033]. 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 acute coronary syndrome, cardiomyopathy, and direct myocardial damage. Patients can also present with life-threatening arrhythmias.[CITATION Mic12 \l 1033] 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 to bolus injections. [CITATION Pol13 \l 1033]

Mechanisms of toxicity

The exact mechanism of cardiotoxicity is unclear, but several theories have been postulated, primarily coronary vasopasm 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 acute coronary syndrome (ACS) with patients complaining of 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 reported normal coronary arteries in these patients on angiography. 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 coronary artery disease, a patient can potentially develop endothelial dysfunction and therefore experience a pathophysiological cascade of events that leads to thrombus formation[CITATION Cwi96 \l 1033]. Further evidence has also been discovered that seems to support a prothrombotic state in these patients. Kuzel et al administered 5-FU in 10 cancer patients 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 [CITATION Kuz90 \l 1033]. 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. Current literature reports several different direct toxic effects. Among those that have been seen are haemorrhagic myocardial infarction, left ventricular hypertrophy with necrosis and apoptosis of the endothelial cells, diffuse myocarditis and sarcoplasmic reticulum dilatation [CITATION Mic12 \l 1033]. These will more often than not give rise to a diffuse area of systolic dysfunction seen on echocardiography or functional imaging.

Treatment

Assuming coronary arteries are normal, treatment is usually conservative, aimed at the underlying coronary vasospasm and resulting left ventricular systolic dysfunction, which normally recovers. Success rates have been reported to be around 70 – 90% [CITATION Mic12 \l 1033]. 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.

Pre-medication with calcium channel blockers to prevent coronary vasospasm has not proven to be of benefit as demonstrated by Eskilsson et al in which Verapamil 120 mg three times a day was administered prophylactically [CITATION Esk90 \l 1033]. 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.

Conclusion

In summary, 5-FU cardiotoxicity is a rare yet important side effect of its use. Its efficacy in dealing with gastrointestinal malignancies will ensure it retains its place as a favoured chemotherapy agent in this setting. Despite not having a pre-existing cardiac history, patients can present to the hospital with life threatening cardiac symptoms. Awareness of the various underlying mechanisms of cardiotoxicity will assist the clinician in directing treatment along with cessation of the drug. Outcomes are good and the potential reversibility of left ventricular systolic dysfunction in these patients makes its early recognition even more vital in a clinical setting.

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CITATION Esk90 \l 1033 : , (8),