

Acute myocardial infarction following 5-fluorouracil treatment

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5-Fluorouracil (5-FU) is an antimetabolite chemotherapeutic agent that is US Food and Drug Administration (FDA) indicated for use in a variety of neoplasms and is a staple agent in many chemotherapeutic regimens. An important adverse effect of 5-FU is cardiotoxicity. There is a wide spectrum of clinical presentation of 5-FU cardiotoxicity from asymptomatic electrocardiogram (ECG) changes to myocardial infarction that clinicians must be aware of when caring for patients receiving this agent.

A 62-year-old man with a history of hypertension, hyperlipidemia, former heavy tobacco use, coronary artery disease (CAD) with myocardial infarction (MI) resulting in percutaneous intervention (PCI) to the left anterior descending artery (LAD) 10 years prior, and newly diagnosed stage IV pancreatic adenocarcinoma with recent initiation of Chemotherapy presented to the emergency room after suffering Ventricular Fibrillation arrest. Two days prior to presentation, he started palliative chemotherapy with FOLFIRINOX (Folinic Acid, 5-FU, Irinotecan, Oxaliplatin). 5-FU was given as a 400 mg/m² bolus followed by a 2400 mg/m² 46-h continuous infusion that finished shortly before his hospital arrival. Prior to starting chemotherapy, he underwent cardiac evaluation showing a normal electrocardiogram (ECG), a transthoracic echocardiogram (TTE) with mildly reduced ejection fraction (LVEF) of 45%–50%, and a nuclear stress test negative for inducible ischemia.

In the field, return of spontaneous circulation was achieved after one round of resuscitation. Post-resuscitation ECG showed ST segment elevations in leads V1-V3 (Figure 1) suggestive of an acute anterior STEMI. He was pre-treated with aspirin and heparin. Emergent left heart catheterization showed a 100% acute thrombotic lesion of the mid LAD with thrombolys-

is in myocardial infarction (TIMI) 0 flow (very late stent thrombosis). A PCI with a 3.5 × 28 mm drug-eluting stent post dilated with 3.0 × 12 mm NC emerge balloon was performed with subsequent TIMI-3 flow (Figure 2). Dual-antiplatelet therapy was started, and his home beta blocker, statin, and angiotensin receptor inhibitor were continued. He was transferred to the cardiac care unit with an uneventful recovery. While inpatient, chemotherapy was held, and his regimen was subsequently changed to Abraxane/Gemzar after obtaining Cardiology clearance to resume chemotherapy.

5-FU belongs to the fluoropyrimidine family, which is a class of antimetabolite drugs. 5-FU is a common agent used in the treatment of solid malignances. Despite its wide use, 5-FU is associated with undesired cardiotoxicity. The most common 5-FU related cardiac events are ECG changes associated with typical or atypical chest pain; however, acute coronary syndrome including MI, heart failure, arrhythmias, and sudden cardiac death have also been related to 5-FU use.^[1,2] The pathophysiology of 5-FU induced cardiotoxicity is not fully delineated, but the most widely proposed mechanisms include ischemia from coronary vasospasm, vascular endothelial damage, and direct myocardial toxicity.^[3]

The theory of coronary artery vasospasm causing myocardial ischemia has been supported by numerous studies showing that many patients with suspected 5-FU cardiotoxicity lack significant coronary artery stenosis on angiography.^[3] Direct visualization of coronary artery vasospasm on angiography has been observed in some cohorts, albeit inconsistently, suggesting the potential role of vasospasm in 5-FU cardiotoxicity.^[3] In our case, the etiology of ischemia was from a fixed stenotic lesion insinuating a multi-factorial mechanism of cardiotoxicity. An experimental study on rabbits exposed to 5-FU showed

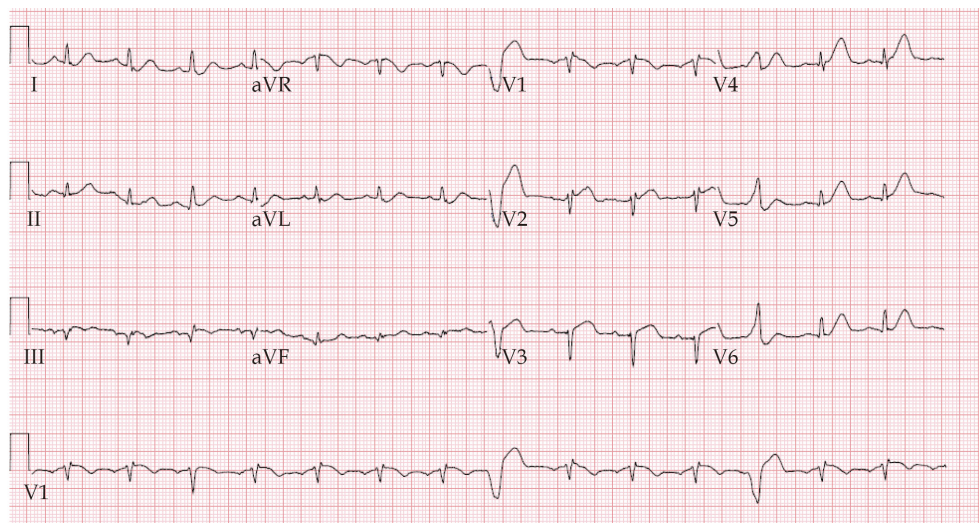


Figure 1 A 12 lead ECG showing an acute anterior STEMI. STEMI: ST-elevation acute myocardial infarction.

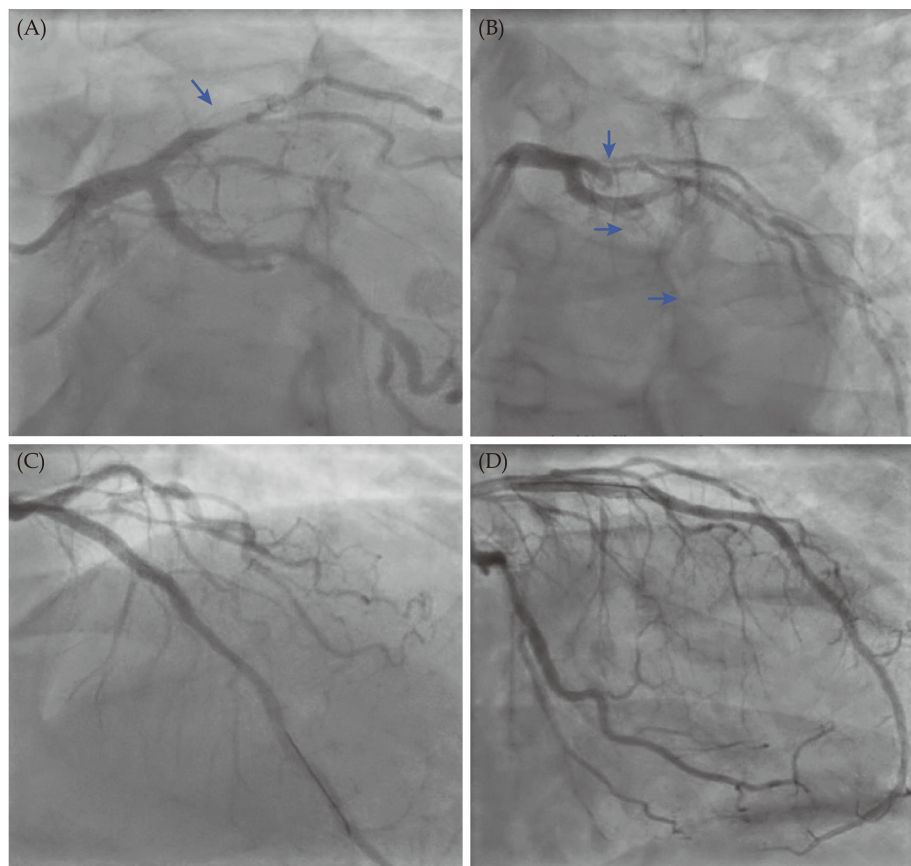


Figure 2 Left Heart Catheterization with mid LAD acute thrombotic occlusion and revascularization. (A): AO caudal view with mid-LAD 100% thrombotic occlusion (blue arrow); (B): LAO cranial view with mid-LAD 100% occlusion (blue arrows showing the LAD occlusion); (C): LAO Cranial view of revascularized LAD lesion (blue arrow); and (D): RAO Caudal view of revascularized LAD lesion (blue arrow). LAD: left anterior descending artery; LAO: left anterior oblique; RAO right anterior oblique.

severe cell damage with accompanying thrombus formation supporting the potential direct cytotoxic effect of 5-FU.^[4] An *in vitro* study on human cardi-

omyocytes and endothelial cells demonstrated increased reactive oxygen species in cardiomyocytes exposed to 5-FU.^[5] These findings support the po-

tential thrombogenic effect of 5-FU secondary to its effect on the endothelium.

The true incidence of 5-FU cardiotoxicity is unknown as there are many confounding variables, such as a standard definition of cardiotoxicity, route and schedule of administration, presence of underlying CAD, concurrent use of other potentially cardiotoxic agents, and the methods and intensity of monitoring patients for signs and symptoms of cardiotoxicity.^[3] The majority of literature is based on retrospective studies with varying definitions of cardiotoxicity, which limits widespread inferences. Reported incidences range from 1%–19%.^[3] 5-FU cardiotoxicity tends to be more common during the first cycle of administration.^[6] Continuous infusion regimens of ≥ 5 days carries the highest risk of toxicity followed by short-term infusion chemotherapy than bolus regimens.^[7,8]

Despite a preceding history of cardiovascular (CV) disease being a suggested risk factor for 5-FU cardiotoxicity,^[2] there is limited data on this population. An analysis of 16 clinical trials performed on 5-FU and its prodrug Capecitabine showed that 81% of studies excluded patients with preexisting CV disease.^[9] As the exact interplay between CV disease and the risk for 5-FU cardiotoxicity is not well defined, there is insufficient evidence to withhold treatment in patients with underlying cardiac disease. Perhaps these patients should undergo closer cardiac monitoring as deemed suitable by their provider, as there are no established guidelines. At minimum, there should be adequate education of potential cardiac symptoms and adverse effects. Despite our patient having an unremarkable pre-chemotherapy cardiac workup, he still suffered a nearly life ending consequence.

If 5-FU related cardiotoxicity is suspected, the first step is immediate drug discontinuation followed by empiric treatment with antianginal therapy such as calcium channel blockers and/or nitrates,^[3] which was shown to abort anginal symptoms in about 70% of patients.^[6] Rechallenging patients with suspected 5-FU cardiotoxicity is controversial. Two important factors that may influence the decision to perform a 5-FU re-challenge is the availability of effective alternative regimens and the intent of therapy (palliative versus curative). In general, re-challenge is not advised due to small studies showing a high risk of cardiotoxicity recurrence associated with sev-

ere morbidity and mortality, up to 13% in one review paper.^[6]

Perhaps underrecognized by clinicians due to the lack of widespread availability, Uridine Triacetate is an FDA approved antidote for fluoropyrimidine toxicity. To date, the largest clinical trial utilizing Uridine Triacetate was in 135 patients with fluoropyrimidine overdose or early onset of severe toxicities.^[10] Complete 30-day recovery was achieved in 96% of patients with 0 mortality in any patient who received the antidote within 96 hours after drug cessation. These findings are promising for Uridine Triacetate as a safe, effective lifesaving antidote against a drug class with potentially fatal toxicities.

5-FU is a staple chemotherapeutic agent that is widely used in the treatment of solid malignancies. Despite its efficacy, cardiotoxicity is a major potential adverse effect that may limit its use. Unfortunately, the exact mechanisms of cardiotoxicity are not well defined. We currently do not have a reliable method to risk stratify patients who may have a higher probability of developing cardiotoxicity, such as those with pre-existing heart disease. Larger scale studies are required to develop evidence-based protocols on monitoring for cardiotoxicity and cardioprotective strategies in patients receiving 5-FU.

REFERENCES

- [1] Sorrentino MF, Kim J, Foderaro AE, Truesdell AG. 5-fluorouracil induced cardiotoxicity: review of the literature. *Cardiol J* 2012; 19: 453–458.
- [2] Labianca R, Beretta G, Clerici M, et al. Cardiac toxicity of 5-fluorouracil: a study on 1083 patients. *Tumori* 1982; 68: 505–510.
- [3] Sara JD, Kaur J, Khodadadi R, et al. 5-fluorouracil and cardiotoxicity: a review. *Ther Adv Med Oncol* 2018; 10: 1758835918780140.
- [4] Cwikiel M, Eskilsson J, Wieslander JB, et al. The appearance of endothelium in small arteries after treatment with 5-fluorouracil. An electron microscopic study of late effects in rabbits. *Scanning Microsc* 1996; 10: 805–819.
- [5] Focaccetti C, Bruno A, Magnani E, et al. Effects of 5-fluorouracil on morphology, cell cycle, proliferation, apoptosis, autophagy and ROS production in endothelial cells and cardiomyocytes. *PLoS One* 2015; 10: e0115686.
- [6] Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf* 2009; 8: 191–202.
- [7] de Forni M, Malet-Martino MC, Jaillais P, et al. Cardi-



otoxicity of high-dose continuous infusion fluorouracil: a prospective clinical study. *J Clin Oncol* 1992; 10: 1795–1801.

- [8] Yuan C, Parekh H, Allegra C, *et al*. 5-FU induced cardiotoxicity: case series and review of the literature. *Cardiooncology* 2019; 5: 13.

- [9] Upshaw JN, O'Neill A, Carver JR, *et al*. Fluoropyrimi-

dine cardiotoxicity: time for a contemporaneous appraisal. *Clin Colorectal Cancer* 2019; 18: 44–51.

- [10] Bamat MK, Tremmel R, Von Borstel R, *et al*. Clinical experience with uridine triacetate for 5-FU overexposure: an update. *J Clin Oncol* 2013; 31(15 Suppl): e20592–e20592.

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