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CHEMOTHERAPY-INDUCED CARDIOMYOPATHY PRESENTING AS CARDIOGENIC SHOCK FOLLOWING 5-FLUOROURACIL THERAPY; A CASE REPORT

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Abstract

Chemotherapy-induced cardiomyopathy spans asymptomatic LV dysfunction to fulminant heart failure. We report a 42-year-old woman with metastatic caecal adenocarcinoma who received two fortnightly cycles of fluoropyrimidine-platinum chemotherapy. She remained well after the first cycle but developed progressive dyspnea and edema seven days after the second, presenting one week later in shock and hypoxemic respiratory failure. On arrival: pulse 130/min, unrecordable blood pressure, SpO_2 88% on room air, elevated JVP, peripheral edema, and basal crepitations. ECG showed sinus tachycardia without ischemic changes. NT-proBNP was 32,300 and troponin-I 2.89; labs revealed hyponatremia and azotemia. Chest radiography demonstrated bilateral infiltrates with mild pleural effusions. Echocardiography showed severe **global** LV systolic dysfunction (LVEF ~15%) with moderate RV dysfunction and a plethoric non-collapsing IVC. Arterial blood gas confirmed type 1 respiratory failure (PaO_2 58 mmHg). Thyroid function was normal; blood and urine cultures were negative. She received non-invasive ventilation, vasopressors, low-dose furosemide infusion, low-dose digoxin and spironolactone, and empiric antibiotics; she subsequently required intubation and intra-aortic balloon pump for refractory shock. Coronary and CT pulmonary angiography were not feasible due to instability. Despite escalation, she suffered cardiac arrest and could not be revived. This case underscores the potential for rapid, fatal cardiotoxicity after fluoropyrimidine-based therapy—even with a normal baseline evaluation—highlighting the need for early recognition, immediate drug cessation, phenotype-directed management, and cardio-oncology pathways.

INTRODUCTION

Chemotherapy-induced cardiomyopathy encompasses a spectrum of cancer-therapy–related cardiac dysfunction, from asymptomatic left-ventricular systolic dysfunction to acute heart failure, myocarditis, arrhythmias, and Takotsubo-like syndromes. Risk varies by agent and host factors: **anthracyclines** show dose-dependent, often irreversible injury ("Type I"), whereas **HER2-targeted agents** classically cause non–dose-dependent, usually reversible dysfunction ("Type II"); other classes—fluoropyrimidines, VEGF/TKIs, immune checkpoint inhibitors, cyclophosphamide—produce diverse phenotypes that do not fit neatly into this binary [1]. Susceptibility is modified by cumulative dose, concurrent/radiation therapy, and baseline cardiovascular risk. Early recognition, immediate modification of oncologic therapy, and initiation of guideline-directed heart-failure treatment are crucial, supported by cardio-oncology pathways emphasizing baseline risk assessment and serial surveillance with ECG, echocardiography, and biomarkers. We describe a previously well 42-year-old woman who developed fulminant biventricular failure and shock one week after her second cycle of chemotherapy

Case Report

A 42-year-old woman, recently diagnosed with metastatic adenocarcinoma of the caecum (local extension to the ascending colon, secondaries to bilateral ovaries, peritoneum, and both lungs – Figure 1) underwent exploratory laparotomy with loop ileostomy and was initiated on mFOLFOX-4 (5-fluorouracil plus oxaliplatin) chemotherapy regimen.

She completed two fortnightly cycles of mFOLFOX-4; while asymptomatic after the first, she developed cardiopulmonary symptoms seven days after the second and presented to our hospital one week later. She developed exertional dyspnea that progressed from grade 2 to grade 4 NYHA over several days associated with orthopnea. This was accompanied by a dry cough for one week, 4–5 episodes of non-bilious, non-bloody vomiting per day for five days, progressive bilateral pedal edema and facial puffiness over one week, and reduced urine output beginning the day before admission. She denied history of chest pain, palpitations, syncope, hemoptysis, abdominal distension, or history suggestive of intercurrent infections. Ileostomy output decreased marginally in keeping with poor oral intake. Concomitant medications were supportive (acetaminophen, antiemetics, vitamin supplements). She reported no similar symptoms after 1st cycle of chemotherapy. Baseline pre-chemotherapy ECG and transthoracic echocardiography were normal, including no regional wall-motion abnormalities and a left ventricular ejection fraction (LVEF) of 58%. She had no known comorbidities or substance use.

On arrival, she appeared irritable and dyspneic. Pulse was 130/min; blood pressure was not recordable; respiratory rate 34/min; room-air SpO_2 88%. Peripheries were cold; jugular venous pressure elevated - 12 cm H_2O. Bilateral pitting pedal edema and periorbital puffiness were present. Lungs had bilateral air entry with basal crepitations. The abdomen was distended with shifting dullness. Neurologic examination found no focal deficits.

Initial investigations showed sinus tachycardia on ECG without ischemic ST–T changes and a non-prolonged QTc. Cardiac biomarkers were markedly elevated: NT-proBNP 32,300; troponin-I 2.89; CK-MB 4.37; LDH 1,716 U/L. Complete blood count revealed hemoglobin 11.5 g/dL, WBC 6,370/µL (ANC 5,010/µL), RBC 4.81×10^6/µL, and platelets 1.99×10^5/µL.Serum electrolytes were unremarkable. Other biochemical parameters revealed - azotemia (urea 188.2 mg/dL; creatinine 2.0 mg/dL), hyperuricemia 10.9 mg/dL, albumin 3.0 g/dL, and total calcium 7.7 mg/dL. Liver enzymes and bilirubin were within reference ranges (AST 24, ALT 29, ALP 73, GGT 35; total bilirubin 1.0 mg/dL; direct 0.3 mg/dL). Thyroid function tests were normal. Blood and urine cultures subsequently returned negative. Chest radiography showed bilateral diffuse infiltrates with mild pleural effusions. Transthoracic echocardiography (Figure 2) demonstrated severe global LV systolic dysfunction with LVEF ~15%, gross LV dilatation, moderate RV dysfunction, mild–moderate pulmonary artery hypertension, mild tricuspid regurgitation, and a plethoric inferior vena cava measuring 2.4 cm without respiratory collapse.

The rapid evolution of cardiopulmonary symptoms one week after fluoropyrimidine-containing chemotherapy, previously normal ECG/echo, markedly elevated natriuretic peptide and troponin, bilateral pedal edema/bilateral lung infiltrates and auscultatory crepitations, elevated JVP, global LV hypokinesia with RV dysfunction, and a plethoric non-collapsing IVC most strongly supported acute chemotherapy-associated cardiomyopathy with decompensation to cardiogenic shock—most plausibly fluoropyrimidine-related. Alternative causes (thyroid disease, septic cardiomyopathy) were less likely given normal TFTs and negative cultures.

She was started on non-invasive ventilation. The initial arterial blood gas on room air showed type 1 respiratory failure. Because of severe hypotension, vasopressor/inotropic support were escalated maintaining a mean arterial pressure near 70 mmHg, and a subclavian central venous catheter was placed. Given clinical congestion, a low-dose furosemide infusion was commenced, with steady urine output around 50 mL/h. Low-dose digoxin and spironolactone were introduced, and empiric broad-spectrum antibiotics were administered. Despite these measures, within next 24 hours hypotension and dyspnea worsened without meaningful laboratory improvement. She was intubated in view of worsening respiratory failure and hemodynamic instability. An intra-aortic balloon pump (Figure 3) was inserted, but her condition continued to deteriorate and she suffered a cardiac arrest from which she could not be revived. Coronary angiography and CT pulmonary angiography were not pursued because of profound hemodynamical instability. Obstructive coronary disease and pulmonary embolism could not be definitively excluded in the absence of angiography/CTPA, but the diffuse biventricular involvement and non-ischemic ECG favored a non-occlusive mechanism.

DISCUSSION

Acute heart failure due to chemotherapy-induced cardiotoxicity is a rare but devastating complication. Our patient's precipitous decline after only two cycles of FOLFOX (5-fluorouracil plus oxaliplatin) underscores that even non-anthracycline regimens can cause severe cardiac injury. Fluorouracil (5-FU) in particular is known to have a wide spectrum of cardiotoxic effects, second only to anthracyclines in incidence [2]. While 5-FU cardiotoxicity classically presents with chest pain from coronary vasospasm, more serious outcomes – including acute dilated cardiomyopathy, arrhythmias, and sudden cardiac death – have been reported [3]. The overall reported incidence of fluoropyrimidine cardiotoxicity varies (around 1–10% of patients, depending on the population and regimen) , with continuous-infusion regimens (such as FOLFOX) carrying a higher risk (up to ~10–18% in some series) than bolus dosing [3]. Overt heart failure is less common – one large study noted symptomatic heart failure in about 2.6% of 5-FU treated patients [4]– but when it occurs, it can be fulminant as in our case.

Mechanisms of Cardiotoxicity: The pathophysiology of 5-FU cardiotoxicity is multifactorial and not yet fully elucidated [3]. Coronary vasospasm is thought to be a primary mechanism: fluoropyrimidines can trigger intense vasoconstriction of the coronary arteries, leading to myocardial ischemia or infarction despite clean coronaries on angiogram. Clinically, this often manifests as angina or acute coronary syndrome-like episodes with ECG changes (ST segment shifts) and troponin elevation, but without obstructive lesions. Elevated levels of endothelin-1 and protein kinase C activation have been implicated in 5-FU-induced vasospasm, and vasodilator therapy (e.g. calcium channel blockers, nitrates) has been reported to relieve the chest pain and ischemic changes, supporting vasospasm as a key factor. Beyond vasospasm, direct myocardial toxicity of 5-FU is also proposed. This is supported by cases of diffuse myocardial dysfunction that do not correspond to any single coronary territory (as in our patient's global biventricular failure). Histologically, animal models have shown 5-FU can cause myocarditis with myocardial necrosis [5]. At the cellular level, toxic metabolites of 5-FU may contribute: for example, fluoroacetate is generated via 5-FU catabolism and can inhibit myocardial aconitase in the Krebs cycle, impairing cardiomyocyte energy production. Patients with partial dihydropyrimidine dehydrogenase (DPD) deficiency (an enzyme that metabolizes 5-FU, found in ~3–5% of people) may be especially susceptible, as reduced clearance of 5-FU leads to higher active concentrations and prolonged exposure [4]. Other proposed mechanisms include endothelial injury and a pro-thrombotic state induced by chemotherapy, which might contribute to microvascular ischemia. In summary, 5-FU likely causes cardiac dysfunction through a combination of acute ischemia (vasospasm), direct myocardial damage (toxic or inflammatory), and possibly metabolic stress, explaining the varied clinical presentations.

Types of Cardiac Manifestations: Fluoropyrimidine cardiotoxicity can mimic many forms of heart disease. Angina pectoris is the most frequently reported symptom, occurring in up to 10–45% of patients in some cohorts (often with transient ECG changes) [6]. More severe ischemic events like myocardial infarction are less common but documented. Our patient's presentation – progressive dyspnea, tachycardia, jugular venous distension with echocardiographic global hypokinesia – is consistent with an acute heart failure/cardiomyopathy picture rather than isolated angina. Indeed, acute left ventricular systolic dysfunction from 5-FU can occur even in patients with no prior heart disease, typically during or shortly after the infusion. Cases of reversible cardiomyopathy due to 5-FU have been described, some recovering normal ejection fraction weeks after stopping chemotherapy[3] . However, not all recover; there are reports of persistent severe dysfunction or relapses if rechallenged. Notably, Takotsubo (stress) cardiomyopathy is one distinct phenotype linked with 5-FU and its oral prodrug capecitabine. Numerous case reports detail patients developing Takotsubo syndrome (transient apical ballooning and wall-motion abnormalities) during 5-FU therapy [7]. This is thought to result from a surge of catecholamines due to the intense stress or pain of 5-FU-induced ischemia, leading to the classic

stress cardiomyopathy pattern. In our patient, the echocardiogram showed severe LV dysfunction (EF ~15%) with moderate RV dysfunction and a dilated IVC, indicating biventricular failure. This global involvement is consistent either with a diffuse toxic myocarditis or a stress cardiomyopathy variant affecting both ventricles. Similar chemo-induced cases have been noted: for example, Lestuzzi et al. reported fulminant 5-FU myocarditis in a patient who acutely developed global heart failure after the first dose of 5-FU. Thus, fluoropyrimidines can cause not only ischemic injury but also a toxic myocarditis/cardiomyopathy, presenting as profound biventricular pump failure.

Oxaliplatin, the other agent in our patient's regimen, is less recognized for cardiotoxicity, but emerging evidence suggests it may have contributed synergistically. Platinum-based chemotherapies (historically cisplatin) are known to increase the risk of vascular events such as hypertension, vasospasm, and myocardial infarction [8]. Oxaliplatin in particular has been associated with rare instances of acute coronary vasospasm and arrhythmias. One reported mechanism is via hypersensitivity reactions: oxaliplatin can trigger a Type I allergic reaction that causes coronary spasm – an entity known as Kounis syndrome (allergic angina). For example, a case in 2011 described a patient who developed coronary vasospastic angina immediately after oxaliplatin infusion, with normal coronaries on angiography (Type I Kounis) [9]. Oxaliplatin has also been implicated in provoking arrhythmias such as bradyarrhythmias and heart block, possibly through autonomic effects or electrolyte disturbances. Yarlagadda et al. (2022) reported a case of third-degree atrioventricular block during oxaliplatin therapy, hypothesizing that oxaliplatin-induced hyperexcitability of cardiac sodium channels and autonomic dysfunction led to coronary spasm and conduction block. Additionally, both 5-FU and oxaliplatin have been noted to prolong the QT interval; cases of torsades de pointes have been observed, especially when combined with other QT-prolonging factors [10]. In our patient, no arrhythmia was documented prior to her collapse, but we cannot rule out an arrhythmic event (ventricular tachycardia or fibrillation) precipitating her cardiac arrest, given that 5-FU cardiomyopathy can be arrhythmogenic. Finally, stress cardiomyopathy can also be triggered by oxaliplatin. Veettil et al. (2024) recently documented Takotsubo cardiomyopathy following oxaliplatin in a patient with colon cancer – notably, that patient had a normal baseline EF and developed acute heart failure during the infusion, very much like our case [11]. In summary, while 5-FU is the more cardiotoxic agent in FOLFOX, oxaliplatin may act as a catalyst – through hypersensitivity-mediated vasospasm or direct effects – further impairing cardiac function.

Management is front-loaded and phenotype-driven. Immediate cessation of fluoropyrimidines is essential, with continuous ECG monitoring, early repeat biomarkers, and prompt echocardiography. Treat vasospasm/ischemia with nitrates and (usually) a non-dihydropyridine calcium-channel blocker. Treat acute heart failure and shock per advanced HF algorithms: oxygen/NIV/intubation as needed; IV loop diuretics for congestion; norepinephrine to maintain perfusion, adding an inotrope (e.g., dobutamine) if low output persists; and early consideration of temporary mechanical circulatory support (IABP/Impella/VA-ECMO) when refractory. Correct aggravating factors—hypoxia, dehydration, electrolyte disturbances (especially K/Mg/Ca)—and manage concurrent AKI. Uridine triacetate is a rescue antidote for fluoropyrimidine overdose or *early-onset* severe toxicity if administered within 96 hours of the last dose; presentations beyond this window derive little benefit. Rechallenge should generally be avoided; if oncologically indispensable, consider inpatient, monitored, bolus-only, dose-reduced 5-FU under nitrate/CCB cover with a strict stop rule at the first symptom. Where feasible, non-fluoropyrimidine alternatives such as raltitrexed or TAS-102 may be considered within oncologic constraints. Programmatically, baseline risk stratification and surveillance (ECG/echo ± biomarkers), optimization of cardiovascular risk factors, and—where available—DPYD-guided dosing help reduce risk and facilitate early recognition.

CONCLUSION

In summary, we report a case of fulminant biventricular heart failure likely precipitated by 5-FU and oxaliplatin chemotherapy. The discussion highlights the proposed mechanisms (coronary vasospasm, direct myocardial toxicity, stress cardiomyopathy, and arrhythmia), the spectrum of cardiomyopathies caused by these agents (from reversible LV dysfunction to cardiogenic shock), and the importance of rapid withdrawal of the chemotherapeutic and supportive therapy. Despite exhaustive measures including inotropes and IABP, our patient succumbed, reflecting the high mortality of this condition when severe. This case underlines the critical need for early recognition of chemotherapy-related cardiac symptoms and prompt, aggressive management – including consideration of mechanical support – to improve chances of recovery. Increased awareness and monitoring will help mitigate such tragic outcomes in the future.

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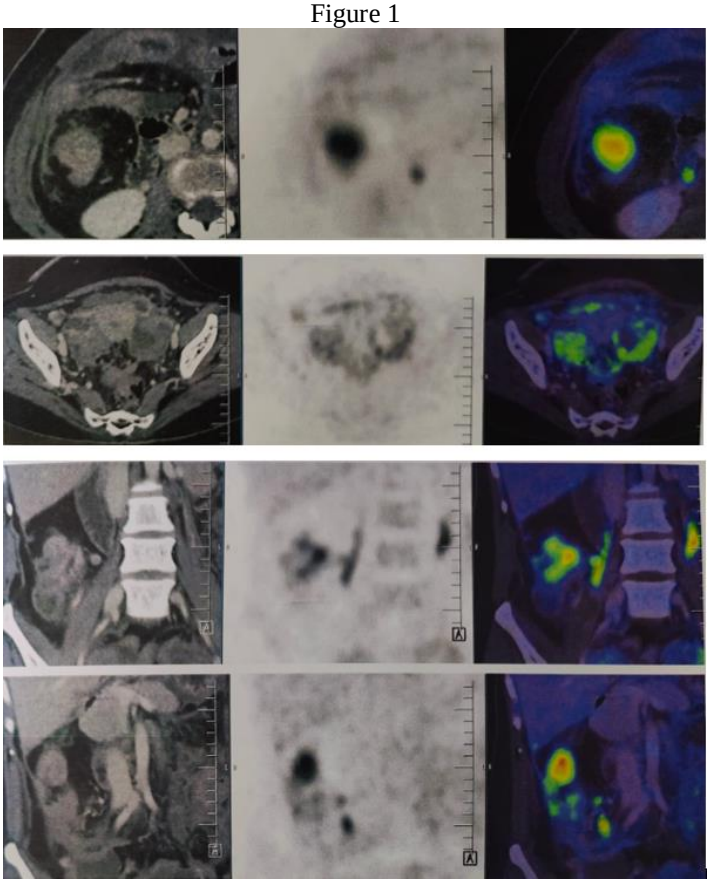
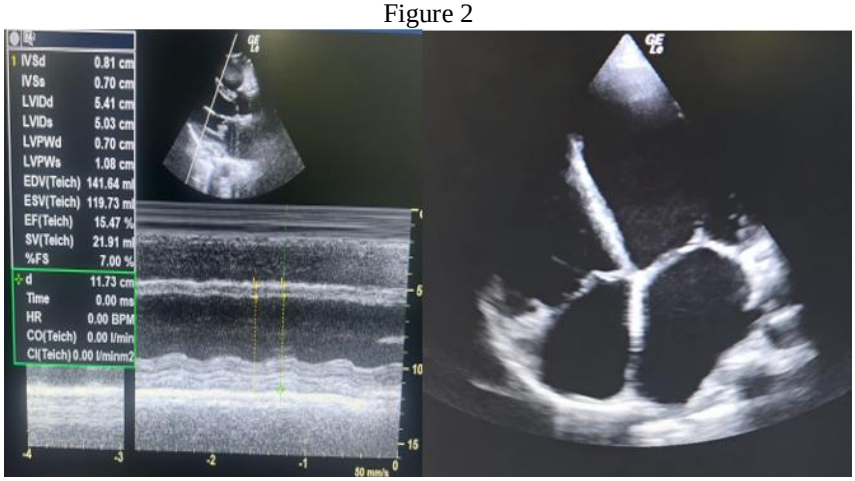
Figure 1



PET CT showed – Malignant lesions involving Ascending colon with secondaries to Bilateral ovaries, Peritoneum, lungs and regional lymphnodes.

Figure 2



Echocardiogram showed global hypokinesia of LV, Severe LV systolic dysfunction with LVEF ~15%, gross LV dilatation with mild dilatation of all chambers, moderate RV dysfunction, mild–moderate pulmonary artery hypertension, mild tricuspid regurgitation, and a plethoric inferior vena cava measuring 2.4 cm without respiratory collapse.

Figure 3

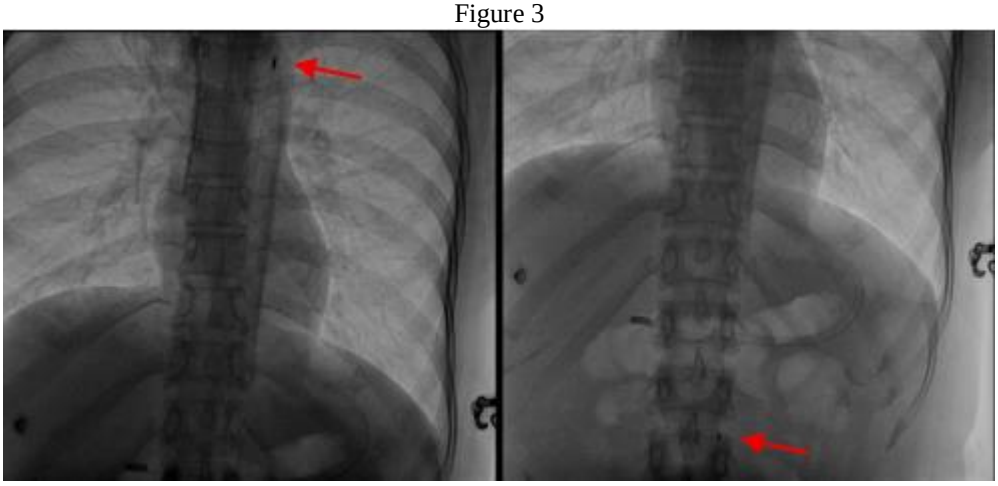


Image showing radio-opaque markers (red arrow) of the Intra aortic Balloon pump placed through trans femoral approach