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# Acute Reversible Cardiomyopathy and Thromboembolism After Cisplatin and 5-Fluorouracil Chemotherapy

## A Case Report

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**ABSTRACT**

Acute development of cardiomyopathy and occlusive thromboembolic events following cisplatin and 5-fluorouracil (5-FU) is rare but frequently lethal. The authors report the successful management of such an event in a 52-year-old man with squamous cell carcinoma of the soft palate. The possible pathophysiological mechanisms are discussed.

### *Introduction*

5-Fluorouracil (5-FU), along with cisplatin, has been widely used as an effective regimen for treating solid tumors. Cardiac toxicity of 5-FU has been described in several medical reports[1-7] and includes arrhythmias, angina pectoris, and myocardial infarction. Acute cardiomyopathy along with thromboembolism[8-10] is a seldom described phenomenon seen during 5-FU and cisplatin therapy. We present here the management of a case of acute reversible cardiomyopathy, left ventricular thrombus, and aortic embolism following 5-FU and cisplatin administration.

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## Case Report

A 52-year-old man was admitted because of extreme fatigue and weakness. He denied nausea, chest pain, or shortness of breath. There were no bowel or bladder symptoms. Two days earlier, he completed the first course of cisplatin (30 mg/m$^2$/day for 3 days), 5-FU (1,000 mg/m$^2$ daily for 4 days), and radiotherapy, for newly diagnosed squamous cell carcinoma of the palate. His history was significant for seizures, controlled with phenytoin. There was no history of heart disease or thrombotic events. He had a 20-pack-year history of smoking.

Physical examination revealed an alert well-oriented man, not in distress, with a pulse rate 90/min, blood pressure 102/68 mm Hg, temperature 100°F, and respiratory rate 18/min. Bilateral submandibular lymphadenopathy and a 4 cm ulcerated lesion on the soft palate were noted. Cardiopulmonary examination was unremarkable on admission. Peripheral pulses were well felt bilaterally. The rest of the physical examination was unremarkable. The electrocardiogram revealed sinus tachycardia and left ventricular hypertrophy with repolarization changes. Cardiomegaly was noted on the chest radiograph. Significant electrolyte abnormalities were found ($Na^+$ 126 mmol/L, $Cl^-$ 91 mmol/L, $K^+$ 3.0 mmol/L, $Mg^{++}$ 1.2 meq/L). Tests of renal function and cardiac enzymes produced normal results.

The patient was treated with intravenous fluids and the electrolyte abnormalities were corrected. A bedside echocardiogram, performed to evaluate the cardiomegaly on the chest radiograph, revealed severely depressed left ventricular function, an ejection fraction of 20%, and a mobile thrombus at the apex (Figure 1).

The patient was immediately given heparin. On the third hospital day, he developed severe pain in the back and both legs. There was bluish discoloration of the feet and absent femoral pulses. A magnetic resonance angiogram of the abdominal aorta documented embolic obstruction at the aortic bifurcation, along with evidence of infarction in the kidneys (Figure 2). There was now evidence of myoglobinuria with elevated creatine kinase enzymes (Total CK=1,032 U/L, MB fraction=8.8 ng/mL, index=0.9 μg/hU) and impaired renal function, with the serum creatinine increasing to 2.6 mg/dL.

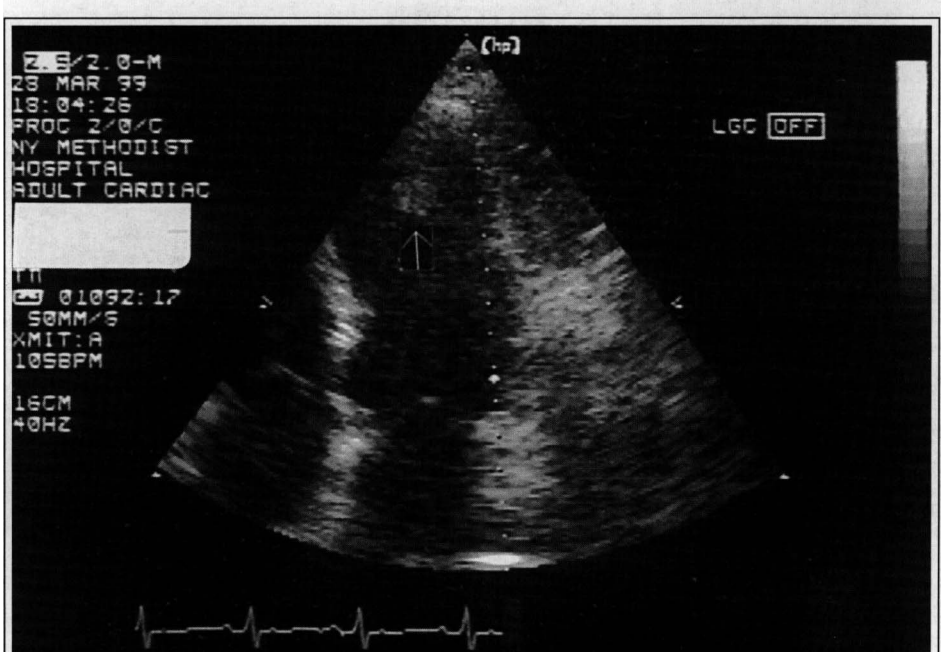


**Figure 1.** Four-chamber view of echocardiogram showing a mobile thrombus in the left ventricle (arrow).

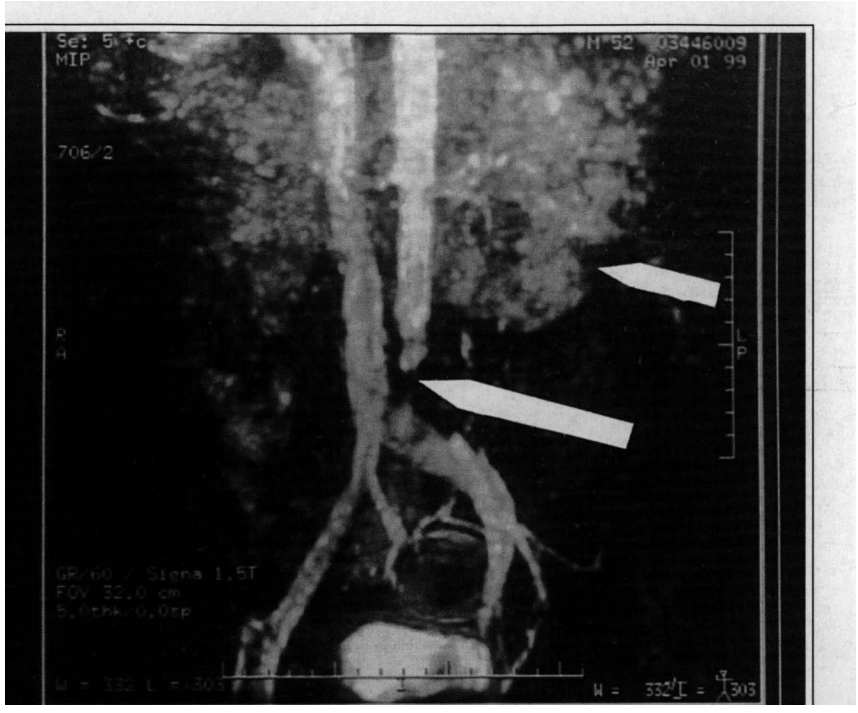


**Figure 2.** Magnetic resonance angiography imaging of the descending aorta showing embolic obstruction at the bifurcation (bottom arrow), along with areas of renal infarction (top arrow).

Bilateral transfemoral thrombectomy was performed, following which circulation to the lower extremities was restored. Heparin was continued throughout the perioperative period, and warfarin was started 24 hours after surgery. Electrolytes were carefully monitored and imbalances corrected. Renal function also improved with a serum creatinine of 1.9 mg/dL on discharge.

A follow-up echocardiogram showed remarkable improvement in left ventricular function with an ejection fraction of 60%. There was complete resolution of the mobile thrombus (Figure 3). He was discharged on a warfarin regimen and followed up as an outpatient.

## *Discussion*

Combined 5-FU and cisplatin chemotherapy is a common regimen for nasopharyngeal, head and neck, and bladder carcinomas. Cardiotoxicity is an uncommon, but well-described side effect of 5-FU, with a reported incidence of 1.6%.[1] It is certainly rare with cisplatin.

The postulated mechanisms for 5-FU cardiotoxicity include direct myocardial ischemia, coronary spasm, and toxic myocarditis from impurities in the preparation. Clinical manifestations include chest pain, diaphoresis, and nausea as well as electrocardiographic changes of myocardial injury.[2] Serial echocardiography before and after treatment cycles has demonstrated a decrease in left ventricular systolic function and impaired diastolic function. These are usually asymptomatic and reversible.[3] There also appears to be a dose-related toxicity with an increased incidence with high-dose continuous infusion therapy. The syndrome appears to be more common on the third or fourth day of infusion or after the third dose but has occurred on initial exposure or bolus injections.[3,4]

Evidence of acute toxic myocarditis has been documented, with histopathologic findings of diffusely scattered areas of necrosis along with an inflammatory exudate. Experimental studies postulate that the accumulation of 5-FU in the myocardium leads to depletion of high-energy phosphate compounds.[5-7]

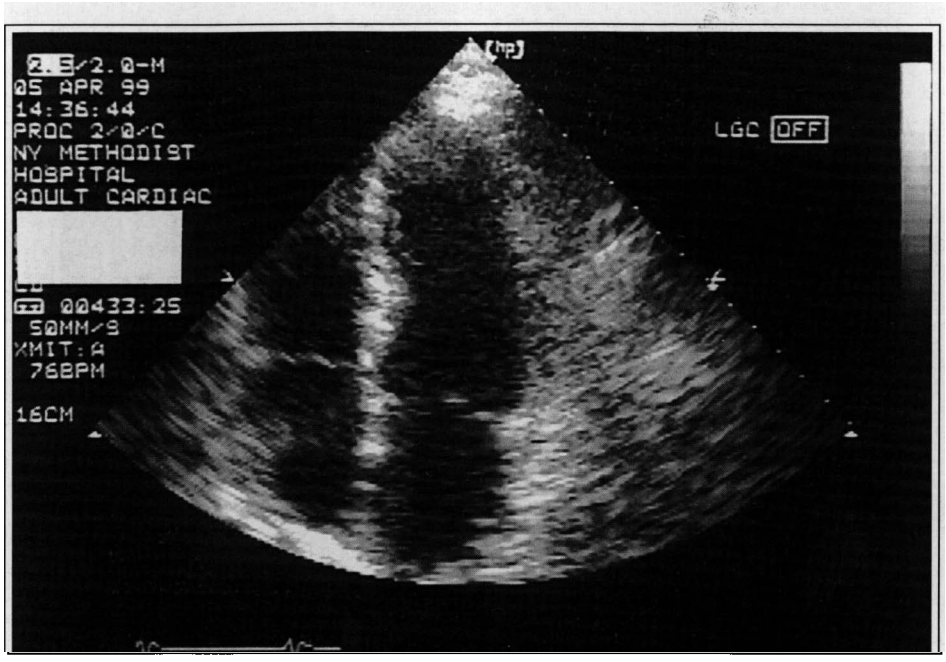


**Figure 3.** Four-chamber view of echocardiograrn a week later with disappearance of the thrombus. Left ventricular function was now near-normal.

Ischemic coronary complications have been reported with cisplatin, with acute endothelial injury, vasospasm, hypomagnesemia, and autoimmune responses being postulated as possible mechanisms.[11-14] Combined 5-FU and cisplatin chemotherapy seems to pose an added risk for cardiotoxicity,[15,16] though 5-FU is believed to be the major contributor to toxicity. Concomitant radiotherapy and preexisting coronary disease appear to be added risk factors for cardiotoxicity. Pottage et al[17] reported that radiation to the chest may sensitize the myocardium for 5-FU cardiotoxicity. Our patient had only localized radiation to the palate, with presumably negligible effect on the heart.

Severe left ventricular dysfunction is a serious complication, with increased incidence of arrhythmias and more treatment-related deaths. Jakubowski et al[18] described a 6% incidence of severe left ventricular dysfunction with combined 5-FU and cisplatin therapy. High-dose continuous infusion therapy of 5-FU, and cisplatin, a commonly used regimen for epidermoid carcinomas of the head and neck, has been implicated as being more cardiotoxic.[8-10] Suprisingly, our patient did not present with the typical symptoms of chest pain, nausea, and electrocardiographic changes but rather with generalized weakness followed by acute thromboembolism. He had no known cardiac illness and his left ventricular function dramatically improved on stopping his medication. This points to an acute toxic and potentially lethal cardiomyopathy.

Successfully treated severe left ventricular dysfunction with intracardiac thrombi and aortic embolization is rather uncommon. In an extensive review of 5-FU cardiotoxicity by Robben et al,[2] the only incidence of a thromboembolic event was a single post-mortem case. Martin et al[19] also have described a necropsy study with startlingly similar circumstances, in a patient with epidermoid carcinoma of the soft palate treated with cisplatin and 5-FU. Most investigators have reported that left ventricular function usually returns to near-normal after discontinuation of therapy. This presents a window of opportunity for a successful outcome. The risk of embolization is highest with a dilated cardiomyopathy.[20,21] Timely anticoagulation may not, however, prevent systemic embolization.[22,23] The development of intracardiac thrombi is presumed to be secondary to the marked left ventricular dysfunction.

There is, however, recent evidence that 5-FU affects red blood cell rheology and induces echinocytosis with increased high shear viscosity. This may contribute to acute thrombotic and occlusive events.[24,25]

## *Conclusion*

We describe here a case of acute reversible cardiomyopathy with an occlusive thromboembolic event. Acute left ventricular dysfunction and heart failure is potentially lethal but is usually reversible and responds to withdrawal of therapy and careful management. Careful correction of electrolyte and fluid balance is mandatory.

Frequent assessment of cardiac function with high-dose 5-FU and cisplatin regimens is strongly advised. Serial echocardiography undoubtedly is of diagnostic and prognostic value.

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## *References*

1. Labianca R, Beretta G, Clerici M, et al: Cardiac toxicity of 5-fluorouracil: A study on 1,083 patients. Tumori 68:505-510, 1982.
2. Robben NC, Pippas AW, Moore JO: The syndrome of 5-fluorouracil cardiotoxicity: An elusive cardiopathy. Cancer 71:493-509, 1993.
3. Patel B, Kloner RA, Ensley J, et al: 5-Fluorouracil cardiotoxicity: Left ventricular dysfunction and effect of coronary vasodilators. Am J Med Sci 294:238-243, 1987.
4. Weidmann B, Jansen W, Heider A, et al: 5-Fluorouracil cardiotoxicity with left ventricular dysfunction under different dosing regimens. Am J Cardiol 75:194-195, 1995.
5. Misset B, Escudier B, Leclercq B, et al: Acute myocardiotoxicity during 5-Fluorouracil therapy. Intensive Care Med 16:210-211, 1990.
6. Sasson Z, Morgan CD, Wang B, et al: 5-Fluorouracil-related toxic myocarditis: Case reports and pathological confirmation. Can J Cardiol 10:861-864, 1994.
7. Porta C, Moroni M, Ferrai S, et al: Endothelin-1 and 5-fluorouracil-induced cardiotoxicity. Neoplasma 45: 81-82, 1998.
8. Celik I, Kars A, Ozyar E, et al: Major toxicity of cisplatin, fluorouracil and leukovorin following chemoradiotherapy in patients with nasopharyngeal carcinoma. J Clin Oncol 14:1043-1044, 1996.
9. Berger C, Chapet S, Reynaud-Bougnoux A, et al: Enhanced acute toxicity in oropharynx carcinoma treated with radiotherapy and concomitant cisplatin, 5-fluorouracil and mitomycin C. Eur J Cancer 32: 1707-1711, 1996.
10. Brillet G, Deray G, Baumelou A, et al: Acute cardiac and renal failure after 5-FU and cisplatin treatment. Nephron 59:667-668, 1991.
11. Tomirotti M, Riundi R, Pulici S, et al: Ischemic cardiopathy from cis-diamminedichloroplatinum (CDDP). Tumori 70:235-236, 1984.
12. Berliner S, Rahima M, Sidi Y, et al: Acute coronary events following cisplatin-based chemotherapy. Cancer Invest 8:383-386, 1990.
13. Ficli I, Handan K, Dilek D, et al: Severe vascular toxicity associated with cisplatin-based chemotherapy. Cancer 72:587-593, 1993.
14. Allerton R: Acute mesenteric ischemia associated with 5-FU, cisplatin, vincristine chemotherapy. Clin Oncol 8:116-117, 1996.
15. Eskilsson J, Albertsson M, Mercke C: Adverse cardiac effects during induction chemotherapy treatment with cisplatin and 5-fluorouracil. Radiother Oncol 13:41-46, 1988.
16. Jeremic B, Jevremovic S, Djuric L, et al: Cardiotoxicity during chemotherapy with 5-fluorouracil and cisplatin. J Chemother 2:264-267, 1990.

17. Pottage A, Holt S, Ludgate S, et al: Fluorouracil cardiotoxicity. Br Med J 1:547, 1978.
18. Jakubowski A, Kemeny N: Hypotension as a manifestation of cardiotoxicity in three patients receiving cisplatin and 5-fluorouracil. Cancer 62:266-269, 1988.
19. Martin M, Diaz-Rubio E, Furio V, et al: Lethal cardiac toxicity after cisplatin and 5-fluorouracil chemotherapy. Am J Clin Oncol 12:229-234, 1989.
20. Meitzer R, Visser C, Fuster V: Intracardiac thrombi and systemic embolization. Ann Intern Med 104: 689-698, 1986.
21. Wllensky R, Jung S: Thromboembolism in patients with decreased left ventricular function: Incidence, risk, treatment. J Cardiovasc Risk 2:91-96, 1995.
22. Stratton J, Resnick A: Increased embolic risk in patients with left ventricular thrombi. Circulation 75: 1004-1011, 1987.
23. Arvan S: Persistent intracardiac thrombi and systemic embolization despite anticoagulation therapy. Am Heart J 109:178-181, 1985.
24. Baerlocher G, Beer J, Owen G, et al: The antineoplastic drug 5-fluorouracil produces echinocytosis and affects blood rheology. Br J Haematol 99:426-432, 1997.
25. Cwikiel M, Persson S, Larsson H, et al: Changes in blood viscosity in patients treated with 5-fluorouracil—a link to cardiotoxicity? Acta Oncol 34:83-85, 1995.