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Cardiac Manifestations with Chemotherapeutic Agents: 5 Fluorouracil-Induced Coronary Artery Vasospasm

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Abstract

5-fluorouracil (5-FU) is a fluorinated, pyrimidine analog, antineoplastic agent that is used in the treatment of several solid organ cancers. Cardiotoxicity is uncommon but life-threatening manifestations such as myocardial infarction may manifest owing to 5-FU-induced coronary artery spasm. Administering smaller doses of the drug, more frequently than not, decreases the risk of cardiotoxicity compared to large doses or with continuous infusions. We present a case of ST-segment elevation in a patient without known coronary artery disease who had presented following continuous 5-FU infusion. Coronary angiogram confirmed absence of coronary artery disease and intravenous calcium channel blockers administration was commensurate with the patient's improvement in symptoms. We discuss the literature on 5-FU and its association with coronary artery spasm, and also briefly review chemotherapy-induced cardiotoxicities to help better prepare internists and other primary health care providers to face similar challenges, particularly of the uncommon but potentially life-threatening manifestations.

Keywords

5-Fluorouracil, Chemotherapeutic Agent, Cardiotoxicity, Vasospasm

1. Introduction

Cardiotoxicity refers to any heart damage arising from cancer treatment. While not common, cytostatic antibiotics of the anthracycline class are perhaps the best

known of the chemotherapeutic agents that induce such manifestation. In addition, certain alkylating agents such as cyclophosphamide, ifosfamide, cisplatin, carmustine, busulfan, chlormethine and mitomycin have also been associated with cardiotoxicity.

5-fluorouracil (5-FU) is a fluorinated, pyrimidine analog that is commonly used as an antineoplastic agent in the treatment of several solid organ cancers [1]. Although uncommon, myocardial infarction is one clinical presentation that may manifest. Management of such a cardiotoxicity is, however, different from that of an acute coronary syndrome. Indeed, the underlying mechanism is often coronary artery spasm. It is, therefore, imperative that clinicians who are responsible for patients on 5-FU be aware of this potential association. We present a case of ST-segment elevation in a patient without known coronary artery disease who had presented following continuous 5-FU infusion.

2. Case Scenario

A 71-year old male, who was receiving chemotherapy for esophageal adenocarcinoma, presented to the emergency department with a severe, crushing, non-radiating, substernal chest pain that was associated with nausea, vomiting and light-headedness. A myocardial perfusion scan one-month prior had been normal. Focused physical exam was unremarkable and in particular, did not suggest evidence of pericardial tamponade. A 12-lead electrocardiogram (ECG) demonstrated new ST-segment elevations in leads I, aVL, V5 and V6 (Figure 1 and Figure 2). He was given aspirin, nitroglycerine, a beta-adrenergic blocker and a 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitor ("statins") in addition to

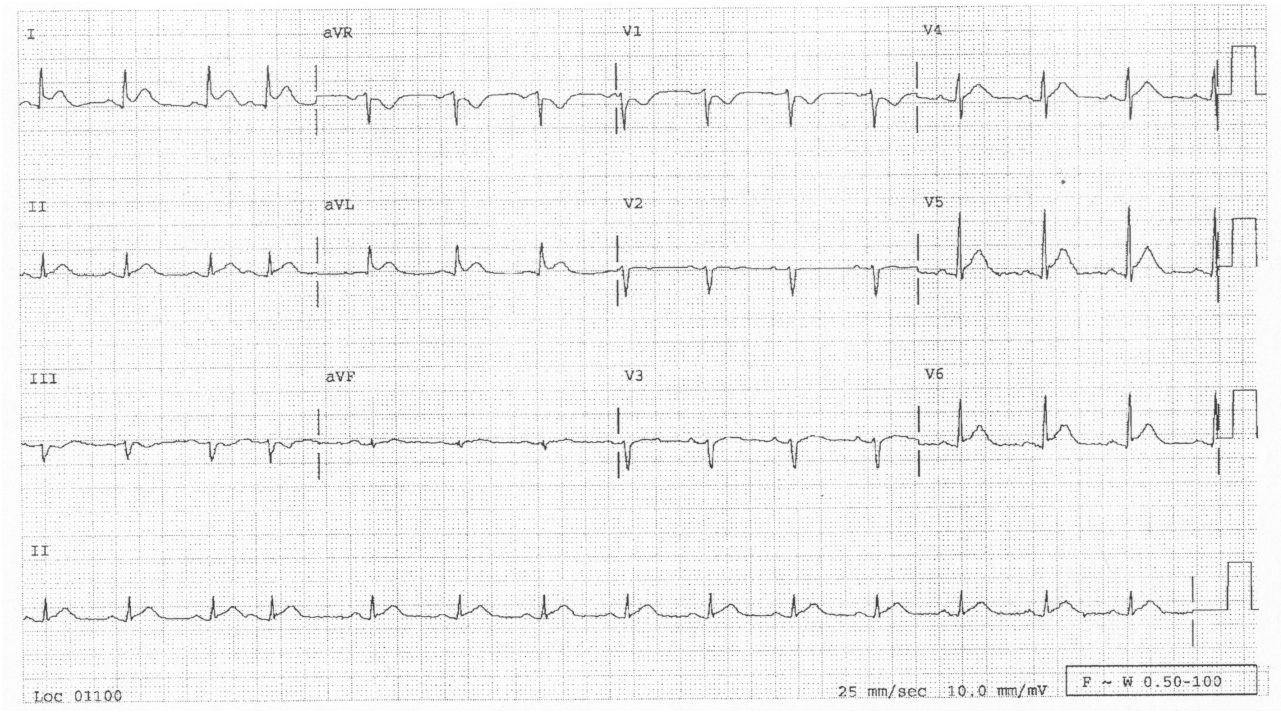


Figure 1. Normal baseline electrocardiogram of the same patient from 2 years before.

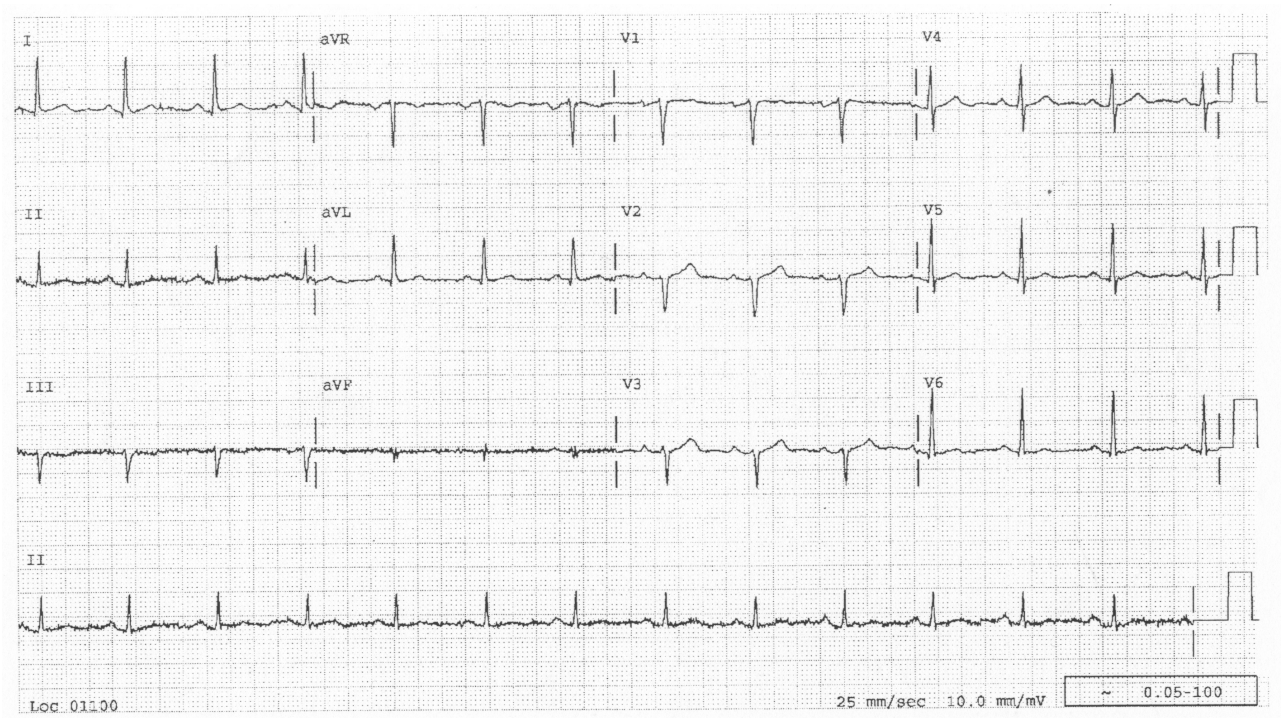
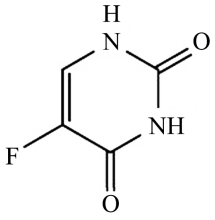


Figure 2. Electrocardiogram of patient that was obtained during symptoms showing ST-segment elevation in leads I, aVL, V5 and V6.

intravenous heparin and eptifibatide. His cardiac biomarkers, however, remained unremarkable. When it was learnt that the continuous neo-adjuvant chemotherapeutic infusion was actually 5-FU (Adrucil, SP Pharmaceuticals Albuquerque, NM), coronary artery vasospasm, likely of the left circumflex coronary artery, was suspected. The 5-FU, heparin and eptifibatide infusions were discontinued. The beta-adrenergic blocker was substituted for a calcium channel blocker regimen which was commensurate with the patient's improvement in symptoms. Coronary angiography following recurrence of symptoms with associated, similar ST-segment changes, neither demonstrated significant coronary artery disease nor coronary artery vasospasm. Left ventricular function on left ventriculogram was preserved without wall motion abnormalities. Symptoms resolved following up-titration of his calcium channel blocker medication and he was subsequently discharged without further recurrence.

3. Discussion and Conclusion

5-FU (**Figure 3**) is a fluorinated, pyrimidine analog, antineoplastic agent that is used in the treatment of several solid organ cancers including colon, head and neck, breast and rectal cancers [1]. Its modus operandi rises from its ability to block the methylation reaction of deoxyuridylic acid to thymidylic acid in the anabolic pathway [2] [3]. This also results in impaired synthesis of deoxyribonucleic acid (DNA) and to a lesser extent, ribonucleic acid (RNA), both essential elements for cell division and growth. Common side effects or toxicities that result from free radicals in a cascade of unbalanced growth and cellular death are



FLUOROURACIL

Figure 3. Molecular structure of 5-fluorouracil.

similar to those associated with other chemotherapeuric agents such as gastrointestinal (nausea, vomiting, diarrhea and esophagitis), dermatologic (dermatitis and alopecia) and hematologic (leucopenia) [1] [3]. Unlike that associated with, synonymously perhaps, certain chemotherapeutic agents, mainly doxorubicin, where incidence of cardiovascular complications are frequent [4], cardiotoxicities with 5-FU are less common (**Table 1**) [5] [6] [7]. Usually, such side effects are dependent on the dose and method of administration [4] [8]. Rapid administration may result in high serum concentrations that may cause more cardiac toxicity than the same amount of drug given over a longer period of time. Administering smaller doses of the drug, more frequently than not, decreases the risk of toxicity compared to large doses at longer intervals or with infusions [8]. The efficacy of 5-FU may also sometimes be altered by certain foods, such as mushrooms (*Lentinus edodes*) [9] and vitamins (Vitamin A) [10].

The incidence of cardiac complications with 5-FU is low, where severe or life-threatening cardiac symptoms can occur in <1% of patients [3] [4] [5] [6]. A wide spectrum of presentations has been reported, including acute myocardial infarction, dysrhythmias and ECG changes, left ventricular dysfunction, cardiogenic shock and sudden death (**Table 1**) [1] [4] [5]. Angiographic evidence of coronary artery spasm has been documented [11]. It is thought to be directly due to the effect of 5-FU on smooth muscle cells as demonstrated by in vitro studies and vasospasm noted during coronary angiography in clinical studies [11]. The underlying mechanism of coronary vasospasm is, therefore, the likely result of endothelial dysfunction caused by 5-FU and its active metabolites. Endothelial dysfunction culminates from an increase in the release of endothelin-1, a vasoconstrictor, and a decrease in the release of prostacyclin, a vasodilatator 5-FU-associated cardiotoxicity has been reported in patients with and without a prior history of cariovascular disease. However, Meyer *et al.* [7] noted that among 483 patients who were followed for one cycle of 5-FU infusion, those with preexisting cardiovascular disease were at higher risk for coronary artery spasm (relative risk 6.83; $p = 0.0023$). In addition, there is data to suggest that concomitant chemotherapy, especially with etoposide and also radiotherapy increases the incidence of this adverse event (**Table 2**). Therefore, the potential for cardiotoxicity should be recognized well in advance, prior to initiating chemotherapy. Patients should be appropriately screened for risk factors and predisposing conditions (**Table 2**) should be modified or if significant, corrected promptly.

Table 1. Common chemotherapeutic agents* and their associated potential cardiovascular toxicities**.

Myocardial or pericardial inflammation:	• Daunorubicin (Cerubidine®) • Pegylated liposomal doxorubicin (Doxil®) • Cyclophosphamide (Cytoxan®, Neosar®) • Cytarabine (Cytosar®)
Cardiomyopathy (left ventricular dysfunction):	• Daunorubicin (Cerubidine®) • Pegylated liposomal doxorubicin (Doxil®) • Epirubicin (Ellence®) • Idarubicin (Idamycin®) • Trastuzumab (Herceptin®) • Mitomycin-C (Mutamycin®) • Cyclophosphamide (Cytoxan, Neosar) • Mitoxantrone (Novantrone®) • 5-Fluorouracil (Adrucil®)
Myocardial/endocardial fibsosis:	• Busulfan (Busilvex®, Busulfex®, Myleran®)
Coronary artery spasm, myocardial ischemia ("steal") or infarction	• Cisplastin (Platinol®) • 5-Fluorouracil (Adrucil®) • Vinblastine (Velbe®) • Vincristine (Oncovin®) • Etoposide (Etopophos®, Vepesid®)
Heart rate or rhythm disturbances:	• Arsenic trioxide (Trisenox®) • Daunorubicin (Cerubidine®) • Denileukin diftitox (Ontak®) • Gemtuzumab ozogamicin (Mylotarg®) • Idarubicin (Idamycin®) • Melphalan (Alkeran®) • Octreotide (Sandostatin®) • Oprevelkin (Neumega®) • Paclitaxel (Taxol®) • Tretinoin (Vesanoid®) • Amsacrine (Amsidine®) • Fluorouracil (Adrucil®)
Hypotension:	• Interleukin-2 (Proleukin®) • Daunorubicin (Cerubidine®) • 5-Fluorouracil (Adrucil®)

* generic and trade names are included only to facilitate ease of recognition among physicians, and have no bearing on efficacy or risk of associated potential cardiotoxicities of one drug over another. ** often when the conventional dose is exceeded above the-rapeutic range or method of administration involves longer duration or continuous infusions.

Table 2. Risk factors that may predispose to development of cardiotoxicities under certain conditions*.

Advanced age	
Female gender	
Concomitant administration of cardiotoxic agents	• Etoposide (Etopophos®, Vepesid®)** • Daunorubicin (Cerubidine®)**
Pre-existing cardiovascular disease	• Significant coronary artery disease • Diffuse or multiple corronary artery lesions • Recent radial artery coronary artery bypass grafting • Those already requiring a calcium channel blocker or nitrates to control vasospasm or angina

Continued

Radiation	• Mediastinal • Chest • Neck
Cumulative dosing regimens:	• Daunorubicin (Cerubidine®)** • Epirubicin (Pharmorubicin®)** • Mitomycin-C (Mutamycin®)**
Maximal or total dose administered during a day/course:	• Cyclophosphamide (Cytoxan®, Neosar®)** • Ifosfamide (Mitoxana®)** • Carmustine (BiCNU®)** • 5-Fluorouracil (Adrucil®)** • Cytarabine (Cytosar®)**
Rate of administration:	• Daunorubicin (Cerubidine®)** • Ifosfamide (Mitoxana®)** • 5-Fluorouracil (Adrucil®)**
Prior chemotherapy and/or cardiotoxicity:	• Daunorubicin (Cerubidine®)**
Electrolyte imbalances	• hypokalaemia • hypomagnesaemia • hypophosphatemia

* often when the conventional dose is exceeded above therapeutic range or method of administration involves longer duration or continuous infusions. ** generic and trade names are included only to facilitate ease of recognition among physicians, and have no bearing on efficacy or risk of associated potential cardiotoxicities of one drug over another.

Those at higher risk, such as those with vulnerable cardiovascular conditions that may not be amenable to aggressive treatment or intervention, should be closely monitored during such chemotherapeutic regimens with perhaps smaller boluses of the particular drug [7] [8]. Early recognition in this particular case prompted the discontinuation of the 5-FU that possibly prevented further complications. It is, therefore, imperative that internists and other primary health care providers be aware of chemotherapeutic cardiotoxicities, particularly uncommon but potentially life-threatening manifestations, such as that with 5-FU.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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