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5-Flourouracil Cardiotoxicity – An Elusive Cardiopathy: Case Report

G. M. Bhat, M. H. Mir, H. I. Showkat, B. Kasanna, F. Bagdadi, A. H. Sarmast, S. Qadri

Sher-I Kashmir Institute of Medical Sciences (SKIMS), Srinagar, Kashmir

Abstract

5-Flourouracil (5-FU) is an S-phase specific, synthetic pyrimidine antimetabolite. It is a frequently administered chemotherapeutic agent for a variety of malignant lesions, either singly or in multidrug regimens. Its adverse side effects involving bone marrow, skin, mucous membranes, GIT and CNS are well known, whereas its cardiotoxicity is relatively uncommon and occurs in 1.2-18%.

Keywords

5-Flourouracil, Cardiotoxicity, S-phase specific.

Introduction

5-FU is a commonly used chemotherapeutic agent as a part of many cancer treatment protocols particularly in solid tumors. Its cardiotoxicity potential is known but considered uncommon and usually not life threatening. We report 4 cases of GIT malignancy in whom exposure to 5-FU resulted in a coronary vasospasm simulating acute myocardial infarction in two patients and supraventricular arrythmia in two patients.

Case Reports

Case-1: A 60-year old male, smoker, known hypertensive on Amlodipine 5mg controlled, non-diabetic, with no prior history of any cardiac symptoms, was diagnosed as a case of colonic cancer stage III. He was started on adjuvant treatment with Folfox-4 (5FU+CLV+Oxadaplatin). He was cleared by cardiologist after base line ECG and Echocardiography were normal. He tolerated 5 cycles of Folfox-4 well. During the 6th cycle of chemotherapy, while he was on 5-FU infusion, he developed acute onset chest discomfort associated with sweating and palpitations. His base line ECG before starting 6th cycle was normal. During the episode, his ECG revealed evidence of supraventricular tachycardia (PSVT) (Figure 1). He was administered I/V bolus diltiazem 15mg and ECG reverted to normal sinus rhythm. He was put on oral diltiazem 20mg TID. 5-FU infusion was continued and his SVT did not recur.

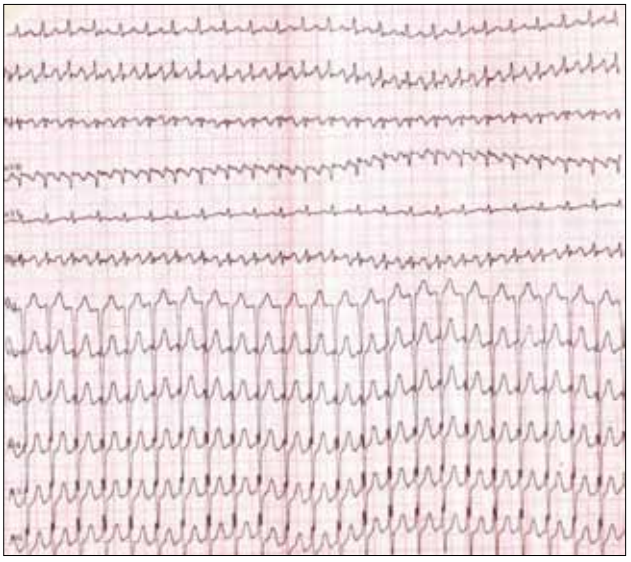

Figure 1. ECG showing supraventricular tachycardia (PSVT)

Case-2: A 52-year old male, non-smoker, normotensive and non-diabetic, with no past history of any cardiac ailment was diagnosed to have adenocarcinoma descending colon with multiple liver metastasis. He was put on palliative treatment with myoclinic regimen in view of poor affordability. He was cleared by cardiologist after base line ECG was normal and normal echocardiography. He received two cycles of chemotherapy uneventfully. During the 3rd cycle, once he was given push dose of injection 5-FU, he started with perspiration and acute onset palpitations. His pulse rate was >150 beats/minute with normal blood pressure. ECG at the time of episode showed PSVT (Figure 2). He was given 6mg of intravenous adensosine

Corresponding author: Dr. Hakim Irfan Showkat, Post-graduate internal medicine, SKIMS, Srinagar, Kashmir, Tel. +91-9419028326, Email: docirfanshahi512@gmail.com

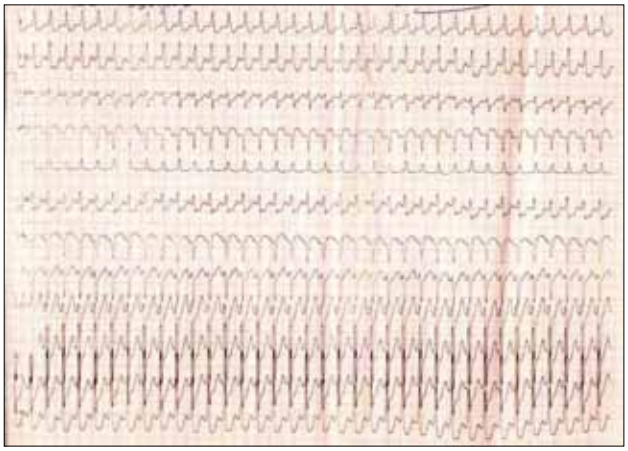

Figure 2. ECG showing supraventricular tachycardia (PSVT)

and reverted to normal sinus rhythm. He was discharged home on 25mg oral metoprolol B.D.

Case-3: A 40-year old male, normotensive, nondiabetic, non-smoker, with no past history of any cardiac symptoms. He was diagnosed as a case of adenocarcinoma stomach. After partial gastrectomy, he was started on FEC chemotherapy protocol. He was cleared by cardiologist after normal base line ECG and normal echocardiography. He tolerated 4 cycles of chemotherapy well. On the 3rd day of his 5th cycle, while he was on 5-FU based chemotherapy, he complained of tightness and pain on left side of chest. His ECG showed ST elevation in leads V1-V3 with T wave inversion in leads II, III and AVF (Figure 3). His trop 'T' done was negative. Echocardiography showed normal LV systolic function and no regional wall motion abnormality. Chemotherapy was discontinued and he was given oral nitrates and oral diltiazem. He was kept under observation for 24 hours. His chest pain settled and ECG changes reverted to normal. Further chemotherapy was abandoned.

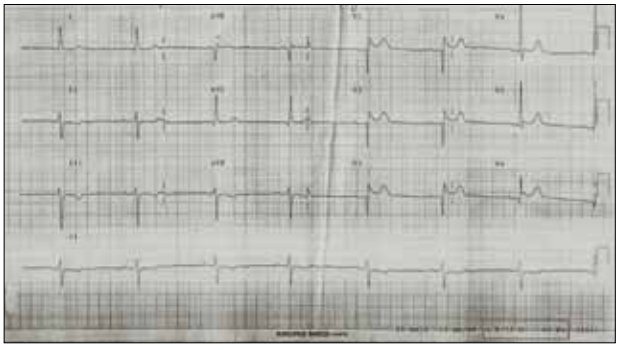

Figure 3. ECG showing ST elevation in leads V1-V3 with T wave inversion in leads II, III and AVF

Case-4: A 65-year old male, hypertensive on 10mg enalapril, chronic smoker and non-diabetic was diagnosed to have adenocarcinoma of gastro-esophageal junction. On laparotomy his growth in the stomach was found to be unresectable. He was advised to go for palliative chemotherapy. His baseline ECG showed LBBB pattern with ST and T wave changes. His baseline echocardiography showed concentric LVH with normal LV systolic function with EF=72%. He was cleared by cardiologist for 5-FU based chemotherapy. He was planned to receive a combination of 5-FU, cisplatin and calcium leucovorin. On the 3rd day of first cycle while he was receiving 5-FU as intravenous volus, he complained of chest pain and burning sensation in retrosternal area. He had profuse sweating with impending doom. His chemotherapy was withheld. ECG showed underlying LBBB with ST rise of 4mm in anterior chest leads (Figure 4). He was shifted to cardiac ICU. Trop "T" was negative. His echocardiography did not show any RWMA. The patient was given full anti-ischemic treatment. For pain, he was put on intravrnous NTG. His repeat trop "T" after 7 hours was also negative. On second day, his coronary angiography was done which showed plaque in LCX with insignificant stenosis (~40%). The patient was discharged after 48 hours from the hospital on anti-ischemic treatment once his pain settled. Repeat ECG showed improvement with reversal of changes. It was presumed that he had suffered acute coronary vasospasm with

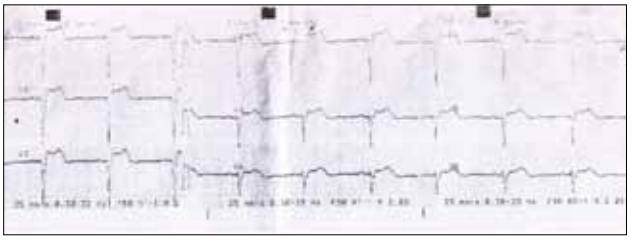

Figure 4. ECG showing LBBB with ST rise of 4mm in anterior chest leads

5-FU treatment as there was no evidence of acute myocardial infarction.

Discussion

The 5-Flourouracil (5-FU) is a frequently administered chemotherapeutic agent used in various malignant neoplasms. Its adverse side effects including diarrhea, mucositis,

neurotoxicity, palm planter dysesthesia and myelosuppression are well-known. Cardiotoxicity is an uncommon adverse effect of 5-FU. Coronary artery spasm has been postulated to be involved in the mechanism of this incidence [1]. Patients may present with angina, myocardial infarction, arrhythmias and even sudden death. There is a high risk of relapse.

Cardiotoxicity due to 5-FU is known to occur in 1.2-18% of patients in different studies [2]. The incidence is higher in those with pre-existing heart disease and in those receiving higher doses. Cardiac events include angina-like chest pain, myocardial infarction, cardiomyopathy, heart failure and arrhythmias [3, 4, 5]. These changes may occur during or shortly after treatment as was seen in our patients, but occasionally, may be delayed for 3 to 18 hours. Although commonly seen with 5-FU infusion, cardiotoxicity can also occur with IV intravenous push doses. In a study, the angina was seen to be the most common manifestation in 89%, followed by ST-T wave changes of ischemia on ECG in 75% and LV dysfunction on echocardiography in 24% [6]. The pathophysiology of 5-FU induced cardiotoxicity is controversial. It is postulated to be mediated by coronary vasospasm and free radical damage to the myocardium [7]. Recent studies support the hypothesis that 5-FU has direct endothelial toxicity resulting in thrombogenic effect and release of vasoactive substances. The clinical manifestations and ECG abnormalities revert to normal once the drug is stopped. Nitrates and calcium channel blockers do not protect against cardiotoxicity [8]. Repeated exposure to 5-FU following an episode of cardiotoxicity carries a higher risk of relapse between 82% and 100% of cases and therefore, it is advised that the drug should not be re-administered in this group of patients [9].

The majority of cardiac adverse events occur during the first cycle of 5-FU. Management consists of discontinuation of the drug, conventional measures for cardiac failure and nitrates. Calcium channel blockers could have a role if the LV function is normal. A recent study indicated that antithrombotic treatment by LMW heparin can protect against the thrombogenic effect of 5-FU [10].

Conclusion

In conclusion, cardiotoxicity is an important, relevant but under-estimated problem in 5-FU treatment. Patients with pre-existing coronary heart disease, electrolyte imbalance and radiation exposure to heart are significantly at increased risk. Routine periodic echocardiography evaluation during 5-FU therapy may not be of value because cumulative toxicity in contrast to other drugs such as Adriamycin is unlikely to occur with this agent, but patients may benefit from continuous ECG monitoring. After a cardiotoxic event, 5-FU should definitely be withdrawn and replaced by an alternative antineoplastic agent.

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