(International Print/Online Journal)

SJIF IMPACT FACTOR: 5.565
PUBMED-National Library of Medicine ID-101739732

ISSN (Print): 2209-2870
ISSN (Online): 2209-2862

International Journal of Medical Science and Current Research (IJMSCR)
Available online at: www.ijmscr.com
Volume 4, Issue 4, Page No: 877-881
July-August 2021

IJMSCR

5-Fluorouracil Induced Asymptomatic Sinus Bradycardia (CTCAE Grade 1)- A Case Report

***Dr. Abiya Jose, [2]Dr.Alin Alex, [3]Dr. Rohan J Mathew, [4]Dr. Amitha Mary John**

[1] PharmD graduate, Nazareth College of Pharmacy, Othera P.O, Thiruvalla, Kerala, India

[2] PharmD graduate, PES College of Pharmacy, 50 Feet Main Rd, Mysore Bank Colony, Hanumanthnagar, Banashankari Stage I, Banashankari, Bengaluru, Karnataka 560050

3Clinical Pharmacist-Department of Hemato-oncology, Believers Church Medical College Hospital, Thiruvalla

[4]PharmD graduate, JKKM College of Pharmacy, Erode

***Corresponding Author:**
***Dr. Abiya Jose**

PharmD graduate, Department of Pharmacy Practice Nazareth College of Pharmacy, Othera P.O, Thiruvalla, Kerala, India

Type of Publication: Case Report
Conflicts of Interest: Nil

Abstract

5-Fluorouracil (5-FU) is one of the most commonly used chemotherapeutic agents particularly in the management of colorectal cancer. Common adverse events of 5-FU include diarrhea, nausea, mucositis, and bone marrow suppression. Although cardiotoxicity is uncommon; sinus bradycardia induced by 5-FU is a rare complication that may turn fatal, if left untreated. We report a 60-year-old woman with adenocarcinoma of the rectosigmoid colon (High-risk stage II) pT3N0Mx lymphovascular invasion (LVI+) who developed bradycardia while receiving 46 hours 5-FU continuous intravenous infusion (CIVI), grade 1 as per the Common Terminology Criteria for Adverse Events (CTCAE). The arrhythmia returned to sinus rhythm after the cessation of 5-FU infusion. The mechanism of 5-FU induced cardiotoxicity is uncertain and there are no prophylactic medications available. If manifestations of cardiovascular anomalies develop, stop the infusion immediately and perform a Cardiovascular workup.

Keywords: Bradycardia, 5-Fluorouracil

INTRODUCTION

5-Fluorouracil (5-FU) is a synthetic pyrimidine antimetabolite that is used as an effective cytostatic agent for various malignancies [(1)]. It is relatively S Phase specific and is converted to fluorodeoxyuridine monophosphate (FdUMP) to form a complex with thymidylate synthase (TS) thereby leading to potent inhibition of deoxythymidine monophosphate (dTMP) resulting in thymine depleted state ("thymine less death"). 5-FU is the mainstay chemotherapeutic agent for colorectal cancer [(2)]. The most common adverse events associated with this drug include diarrhea, nausea, mucositis, and myelosuppression. Although rare, cardiotoxicity can be a serious side effect as well as an infrequent complication of 5-FU chemotherapy [(3)]. Cardiotoxicity due to 5-FU appears to be dosage and schedule-dependent. Patients are often asymptomatic but may exhibit angina, myocardial infarction, Prinz metal's angina, supraventricular arrhythmias, and asymptomatic ST-T wave changes [(3,4)].

We present a 60-year-old woman who developed asymptomatic bradycardia while receiving 48 hours continuous intravenous infusion (CIVI) of 5-FU for adenocarcinoma of the rectosigmoid colon, grade 1 as per the Common Terminology Criteria for Adverse Events (CTCAE). [(5)] We also reviewed the existing

mechanism of action of 5-FU and the various aspects governing its cardiotoxic effects.

Proposed mechanisms of 5-FU induced cardiotoxicity [1,3]	
Spasm of coronary arteries	• Protein kinase C • Endothelin-I
Damage on coronary endothelial cells (Vascular Endothelial Dysfunction)	• Micro thrombotic occlusions resulting from the direct toxic effect of 5-FU on vascular endothelial cells • Oxygen-free radicals
Direct myocardial injury	• Alpha-fluor-beta-alanine (FBAL) (The breakdown product of 5-FU)
Autoimmune mediated cardiotoxicity	

Table 1: -Proposed mechanisms of 5-FU induced cardiotoxicity

CASE PRESENTATION

A 60-year-old hypertensive female presented to the Gastro Surgery Department with complaints of loose stools (increased bowel frequency of 8 times /day) and per rectal bleeding (occasional). She had a history of altered bowel habits for 8 months, belching and, weight loss of about 6 kg in the last 3 months. An initial evaluation in a nearby hospital with ultrasonography (USG) abdomen suggested mild concentric rectal thickening which would be either inflammatory or neoplastic nature and an enlarged uterus showing multiple fibroids.

Furthermore, she was evaluated with contrast-enhanced computed tomography (CECT) of the abdomen which indicated short segment asymmetric circumferential enhancing wall thickening in the rectosigmoid junction with adjacent pericolic fat infiltration and pericolic and inferior mesenteric lymph nodes. These findings were suggestive of carcinoma colon. Her colonoscopy report revealed an ulcer proliferative growth in the rectosigmoid region and carcinoembryonic antigen (CEA) was 1.12. Hence, a biopsy was performed from the rectosigmoid junction growth and the report showed a moderately differentiated adenocarcinoma with mucinous components. Her cancer antigen (CA) 125 level was also elevated (10.31). She underwent low anterior resection (LAR), total abdominal hysterectomy, Bilateral Salpingo-Oophorectomy (BSO), colostomy, double J (DJ) stent. Post-surgery, she was started on Cycle 1 chemotherapy with 5-FU, leucovorin, and oxaliplatin (FOLFOX).

On the 2nd day of her 5th cycle of chemotherapy, she experienced an episode of sinus bradycardia while receiving 5-FU CIVI. Her chemotherapy was withheld then and a Cardiology consultation was sought. Electrocardiogram (ECG) report showed sinus bradycardia. Creatine phosphokinase (CPK), Troponin-I, creatine kinase myocardial band (CPK-MB), complete blood count (CBC) values, and blood biochemical profile (including serum electrolytes) were normal. She had no further episodes of

Volume 4, Issue 4; July-August 2021; Page No 877-881

bradycardia and was closely kept under observation. Her ECG showed no dynamic changes and Troponin-I became negative. However, the patient was stable and chemotherapy was restarted once the bradycardia was resolved after the cardiology clearance.

She was closely monitored for bradycardia events during her 6th cycle of chemotherapy and the dose of 5-FU was reduced to 2500 mg over 46 hours from the previous cycle in which the dose was 3250mg over 46 hours as CIVI. She tolerated the chemotherapy (De Gramont regimen) (7) well, but at the same time bradycardia events had reoccurred during the 7th & 8th cycle, in which the dose was again increased to 3250 mg over 46 hours as CIVI. Although she had persistent bradycardia, there was no evidence of ischemia, hence chemotherapy was withheld and a Cardiology consultation was sought again. Her ECG showed no dynamic changes and Troponin-I was negative. She was treated with Orciprenaline due to the exhibition of persistent bradycardia.

DISCUSSION

Cardiotoxicity is a rare but serious side effect of 5-FU. Although an exact pathophysiological and causal link between this anticancer agent and its cardiotoxic effects remain unearthed, multiple hypotheses including drug-induced coronary spasm, the vasospastic hypothesis, and an immune allergic reaction or a direct toxic effect on the myocardium and pericardium have been implicated [(6)]. The cardiovascular side-effects of 5- FU were first documented by Gaveau in 1969 and Carpenter in 1972 [(7,8)]. Mariam Charkviani et al reported a case on rare presentation of cardiotoxicity related to 5-FU where they support the vasospastic hypothesis of 5-FU cardiotoxicity [(2)].

Talapatra et al reported a series of 207 patients who developed transient asymptomatic bradycardia after being treated with CIVI of 5-FU in the Department of Radiation and Oncology [(4)]. In 2009, Saif et al had reviewed 377 cases of 5-FU-associated cardiotoxicity and found that the majority of cases reported were found in patients receiving CIVI. [(9)]

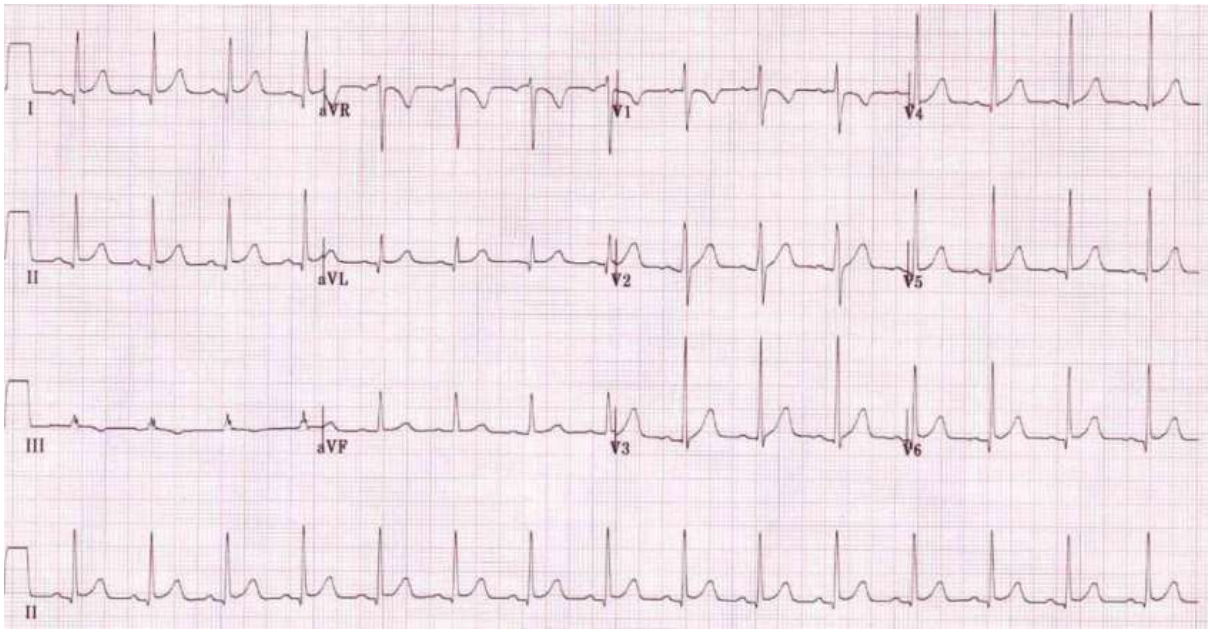

Figure 1: - Patient's ECG before starting chemotherapy.

Volume 4, Issue 4; July-August 2021; Page No 877-881

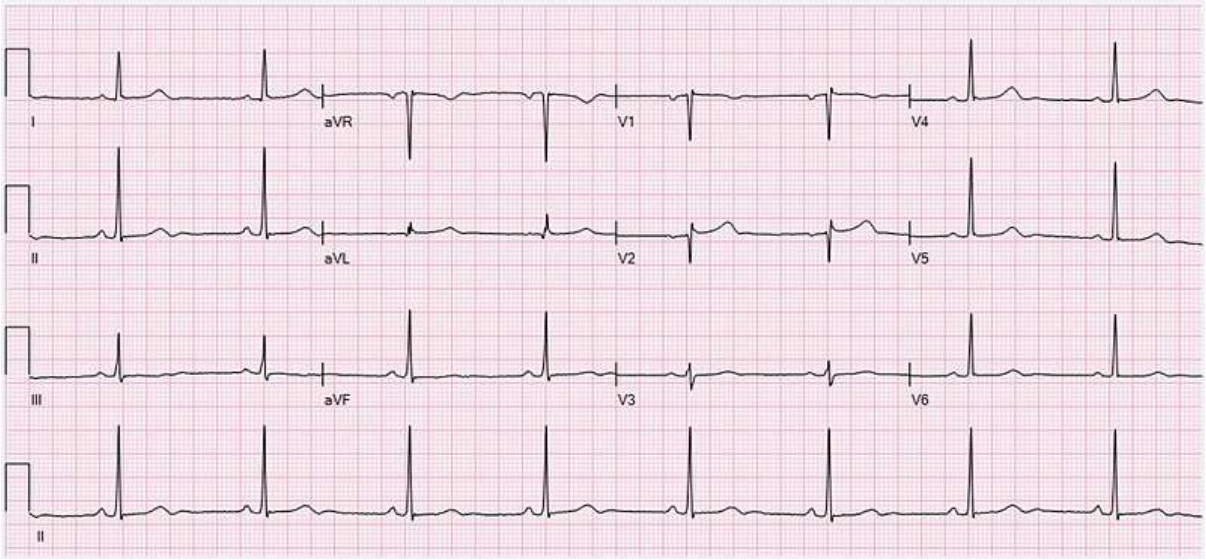

Figure 2: Patient's ECG after the first episode of bradycardia

As to this patient, when bradycardia was noticed during 5-FU infusion, we had discontinued the drug immediately and a cardiology consultation was sought. Chemotherapy was continued after obtaining the clearance. The infusion dose was also reduced to 2500 mg over 46 hours from the previous cycle in which the dose was 3250mg over 46 hours as CIVI. There was a positive rechallenge with 5-FU 3250 mg over 46 hours in the next two cycles elucidating that 5-FU induced sinus bradycardia was dosage and schedule dependent as reported by K. Talapatra et al.

CONCLUSION

We concluded that sinus bradycardia may arise in patients on the CIVI 5-FU regimen based on its schedule and dosage criteria but the exact causal link between 5-FU dosage and cardiotoxicity remains unclear. Moreover, clinicians ought to be vigilant and must focus on close monitoring of patients receiving 5- FU therapy as it may lead to catastrophic effects, if not treated promptly.

ACKNOWLEDGEMENT

Authors are thankful to the God Almighty for the divine grace and blessings in making all these accomplishments made possible. It is our duty to render our heartfelt thanks and gratitude to our beloved parents for their constant support.

CONFLICT OF INTEREST: The authors declare no conflict of interest.

REFERENCES

1. Yuan et al. 5-FU induced cardiotoxicity: case series and review of the literature. Cardio-Oncology (2019) 5:13,https://doi.org/10.1186/s40959-019-0048-32.
2. Mariam Charkviani et.al.Rare Presentation of Cardiotoxicity Related to 5-Fluorouracil Hindawi Case Reports in Oncological Medicine Volume2020, https://doi.org/10.1155/2020/4151474.
3. Chi-Nan Chang, Kai-Chen Wang.5-fluorouracil (5-FU)-induced sinus bradycardia: The Changhua Journal of Medicine 2014;12: 107-110.DOI: 10.6501/CJM.1203.003
4. Talapatra et.al. Transient asymptomatic bradycardia in patients on infusional 5-fl fluorouracil. Journal of Cancer Research Therapy - September 2007;3(3):-169-171
5. Adverse Event Recognition and Management in Practice and on Clinical Trials. Available from: https://jhoponline.com/jhop-issue-archive/2015-issues/march-vol-5-no-1/16335-adverse-event-recognition-and-management-in-practice-and-on-clinical-trials.[Access 10 July 2021]
6. Clavel M, Simeone P, Grivet B. Cardiac toxicity of 5-fluorouracil: Review of the literature, 5 new cases. Presse Med 1988; 17:1675-8.

Volume 4, Issue 4; July-August 2021; Page No 877-881

7. Tutkun I, Nanl S, Caymaz O, Ayanolu E, Duman D. Cardiotoxicity of 5-flourouracil: Two case reports. Auris Nasus Larynx 2001; 28:193-6.
8. Reitemeier RJ, Moertel CG. Comparison of rapid and slow intravenous administration of 5-fluorouracil in treating patients with advanced carcinoma of the large intestine. Cancer Chemother Rep 1962; 25:87-9.
9. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. Expert Opinion Drug Safety. 2009;8(2):191–202.

Volume 4, Issue 4; July-August 2021; Page No 877-881