

Acute coronary syndrome associated with NIGRO protocol in anal cancer.



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ABSTRACT

5-fluorouracil (5-FU) cardiotoxicity is not a common, but with potentially deleterious effects on the patient condition. In this paper we present the case of an 53-year-old woman undergone local resection for localized anal cancer and then she was treated with NIGRO protocol. 48 hours after the end of 5-FU i.v. administration an acute coronary syndrome was developed. The electrocardiogram showed hyperacute T waves in all leads except for V1 and aVL that showed negative T waves in combination with chest pain and diaphoresis promptly resolved after sublingual isosorbide dinitrate. A subsequent coronary angiography was performed and normal coronary arteries were shown. The potential causes and the treatment are being discussing.

KEY WORDS: acute coronary syndrome, 5-FU cardiotoxicity, anal cancer, NIGRO protocol.

INTRODUCTION

Anal malignancies are relatively uncommon, encompassing 1.5% of all digestive system malignancies [1] and 1 to 8% of all anorectal malignancies [2,3] For localized disease, National Comprehensive Cancer Network (NCCN) guidelines recommend 5-fluorouracil (5-FU), mitomycin, and radiotherapy, the so called NIGRO protocol [4]. Based on previous literature from the above chemotherapeutic agents, 5-FU was considered the most cardiotoxic one [5-7].

Specifically, 5-FU may cause acute coronary ischemia and/or cardiomyopathy and it could present with angina, elevated cardiac enzymes, electrocardiogram (ECG) changes [5] but also with arrhythmias, myocardial infarction or sudden cardiac death probably caused by coronary arteries vasoconstriction [6].

In this case report we describe a case of cardiotoxicity in a woman with localized anal cancer treated with NIGRO protocol.

CASE PRESENTATION

A 53 years old woman undergone local resection of localized anal cancer (T1N0M0) and then she was treated with NIGRO protocol which consists of radiation therapy (RT) combined with 5-FU and mitomycin-C administration. The patient had no cardiovascular risk factors or history for cardiac disease. 5-FU is usually administered via intravenous administration over the course of four to five days at the beginning of treatment and repeated after four to six weeks [8]. Mitomycin is also given as an i.v. injection, usually at the start of radiation treatment and then again towards the end, about four to six weeks later [8]. However, during the first cycle with 5FU, the patient complained of chest pain after 48hrs from ending of 5-FU-infusion and then she was admitted in emergency room of our hospital for further investigation.

In the Emergency Room patient complained dyspnea, and acute chest pain. At physical examination we registered a heart rate of 77 beats per minute, a blood pressure of 175/100 mmHg and there were no cardiac murmurs or signs of heart failure. Blood tests had shown normal cardiac enzymes, haemoglobin and renal function. The electrocardiogram (ECG) showed high hyperacute T waves in all leads except for V1 and aVL that showed negative T waves (figure 1). At focused echocardiography left ventricle showed preserved ejection fraction (EF), no evidence of regional wall motion abnormalities, no significant valve regurgitation or

stenosis, no pericardial effusion and the right ventricle showed normal global kinesis. After sublingual administration of 5 mg of isosorbide dinitrate chest pain and hyperacute T waves alterations were resolved (figure 2). The BP shows only a mild reduction in systolic value (160/100 mmHg). Subsequently, the patient was admitted in our Cardiology Intensive Care Unit for careful monitoring. A coronary angiography and ventriculography was performed 12hrs later which has shown no coronary stenosis and normal left ventricular dimensions and function (figure 3,4,5).

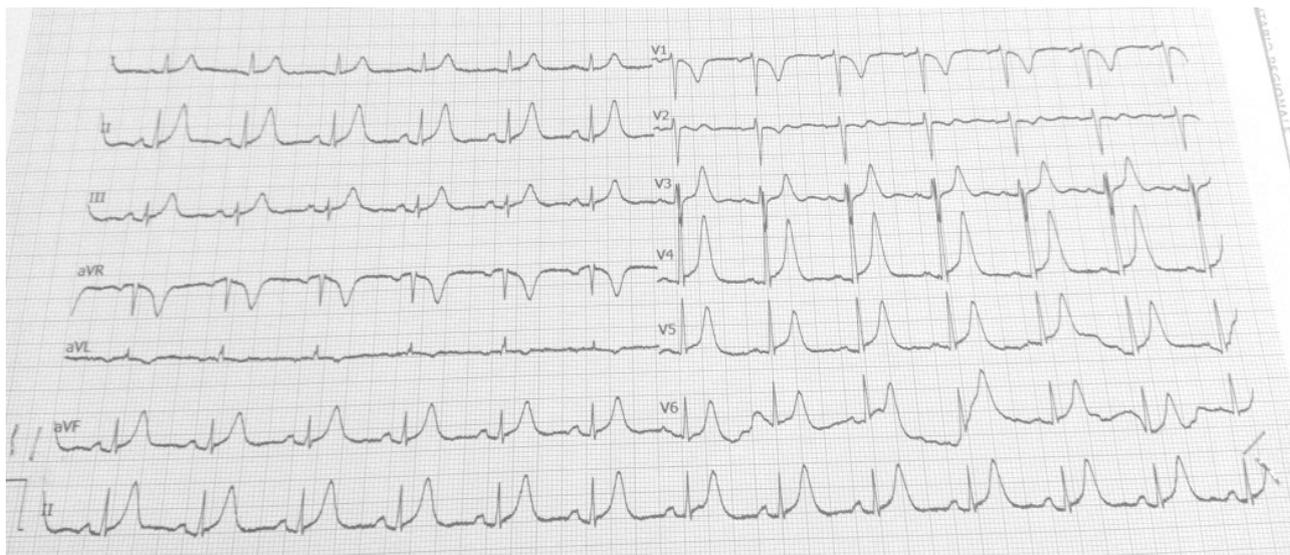


Figure 1. Electrocardiogram of patient in the emergency room. Hyperacute T waves, during chest pain, are observed in the inferior and antero-lateral leads.

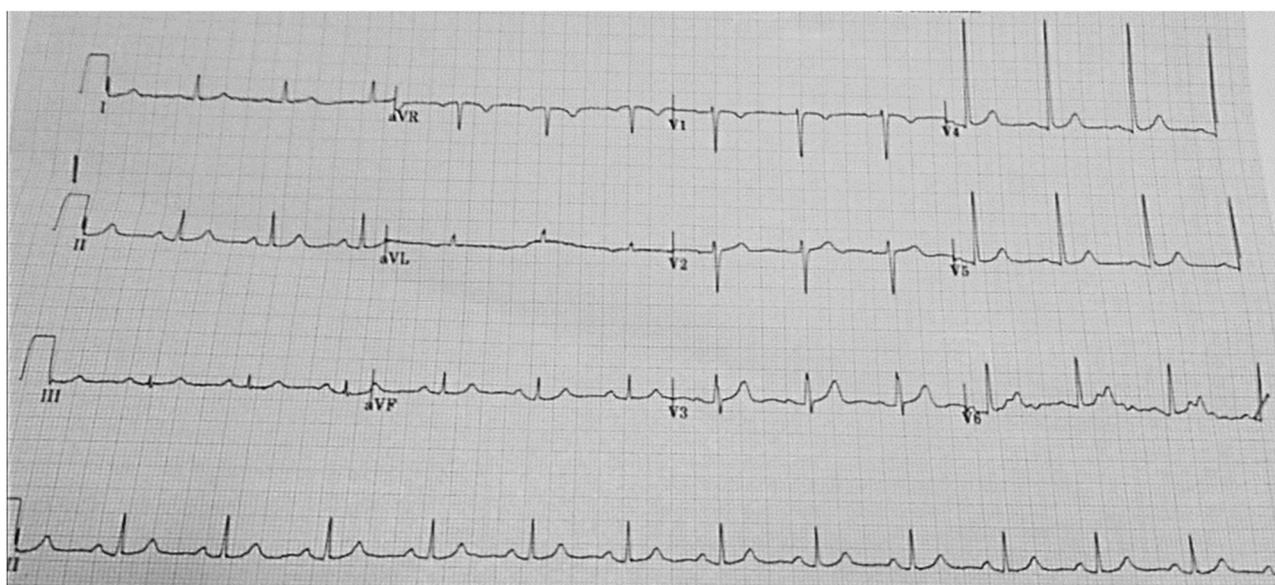


Figure 2. Electrocardiogram of patient in the emergency room after sublingual nitroglycerine administration. A complete resolution of ST changes was observed.

In the second day of hospitalization a therapy with oral administration of diltiazem 180 mg/die and transdermic nitroglycerin patch 5 mg was started. The patient was asymptomatic during the remaining hospital stay and was discharged at the third post-admission day. After oncologist advice the chemotherapy protocol was discontinued and patient was treated with radiotherapy only. Four months later the patient was asymptomatic and there was no new cardiovascular events at cardiac ambulatory evaluation.

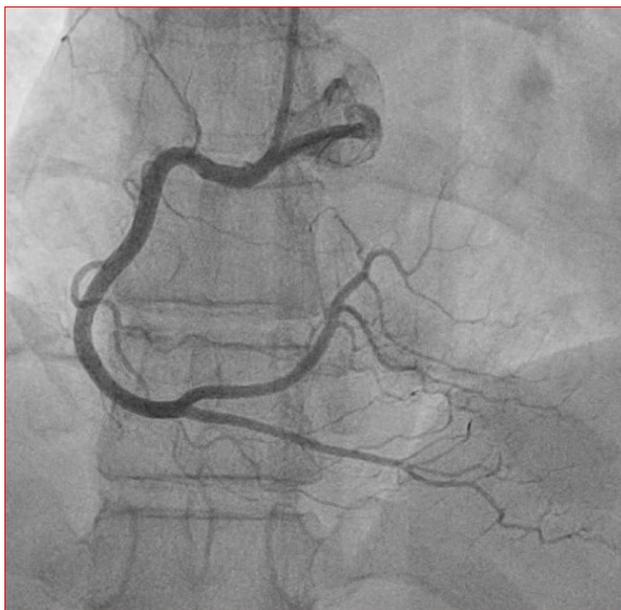


Figure 3. Coronary angiogram of right coronary system. Normal right coronary artery.

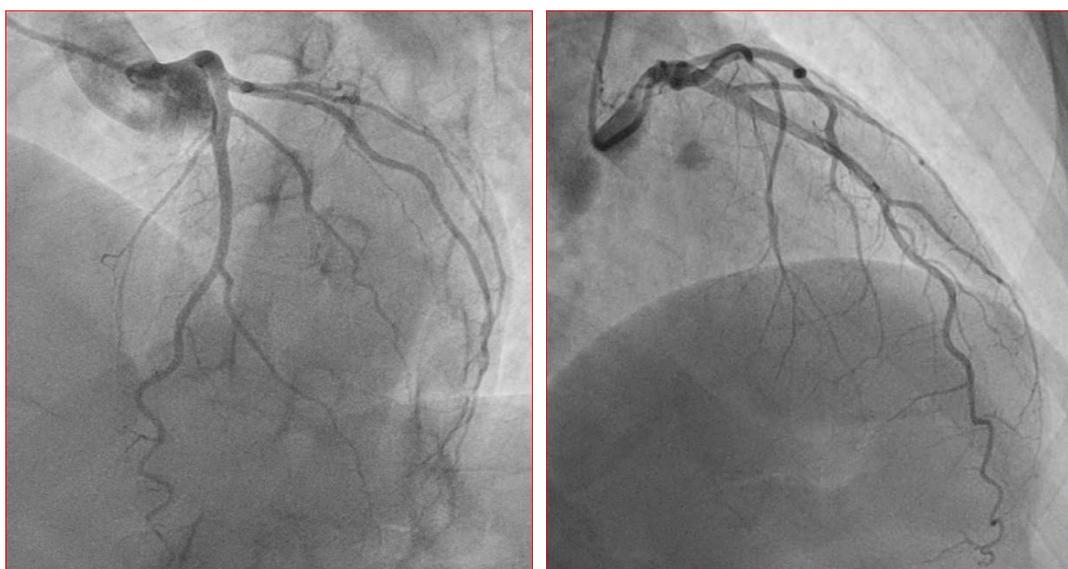


Figure 4. Coronary angiogram of left coronary system. Normal coronary arteries

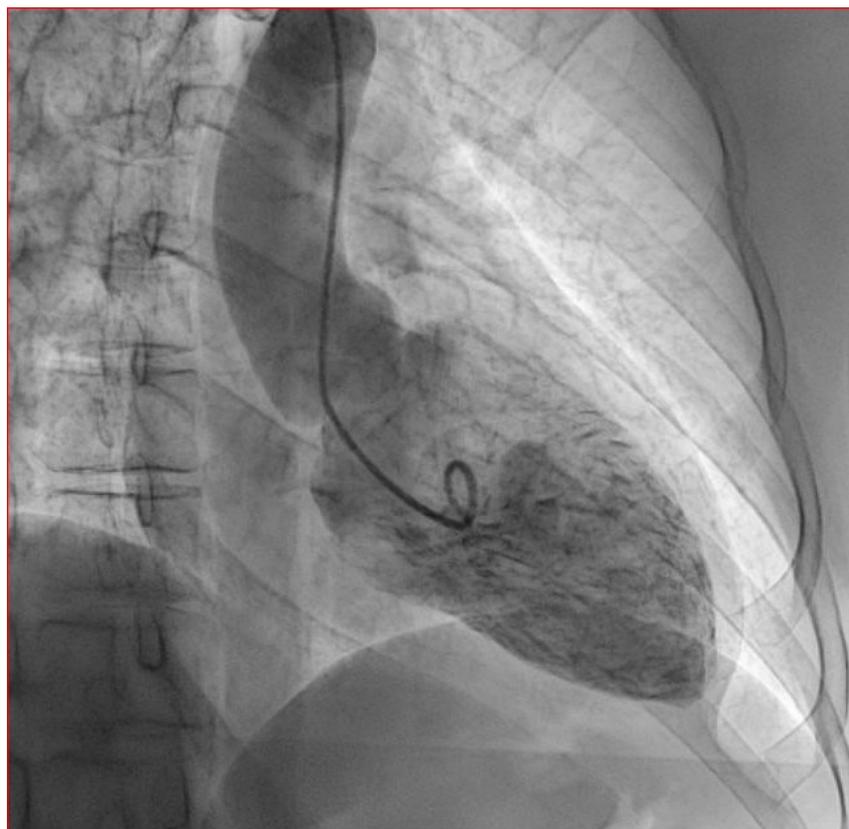


Figure 5. Left ventriculogram with normal dimensions.

DISCUSSION

The above case regards a severe cardiotoxicity in the contest of NIGRO protocol, caused probably by infusion of 5-FU, mimicking acute myocardial infarction occurring in a patient receiving chemotherapy for anal cancer 48hrs from the end of the infusion. On the other hand, it is well known that mitomycin has not any cardiotoxic effect [9] and also it was not administered yet. The symptoms and ECG abnormalities resolved after sublingual administration of isosorbide dinitrate, supporting the vasospastic hypothesis of acute coronary ischemia producing by 5-FU.

It is known that 5-FU, a dihydropyridine derivate, represent the cornerstone of colon-rectal systemic chemotherapy. The toxicity of 5-FU varies from common symptoms like nausea, vomiting, diarrhea, stomatitis, alopecia and leucopenia, to uncommon but serious cardiotoxicity that usually manifest with angina symptoms, elevated cardiac enzymes, electrocardiogram (ECG) changes at various dose levels [5,10],

coronary vasospasm [6], coronary thrombosis, cardiomyopathy and sudden cardiac death [11]. Cardiotoxicity has been reported to occur with 5-FU administered either as a single agent or in combination with other chemotherapy agents [10,12].

Various mechanisms were hypothesized to explain the development of 5FU-cardiotoxicity: arterial endothelial damage and/or dysfunction, increase in the release of endothelin-1 (that has a vasoconstrictor effect) [13], and a decrease in the release of prostacyclin (vasodilator effect). These alterations result in arterial vasoconstriction, platelet aggregation and myocardial inflammation [14]. In some reports, coronary artery vasospasm was directly visualized during coronary angiography [15] and also brachial artery vasoconstriction immediately following the administration of 5-FU injections [16,17]. Previous reports described angina and acute ischemic ECG changes during infusion of 5-FU, resolved after administration of nitroglycerin [18] or diltiazem [19].

In our report, patient symptoms and ECG alterations developed after 48hrs from the 5-FU infusion ending and this could be caused by late release of potent vasoactive 5-FU metabolites, which accumulate over time due to metabolization of 5-FU [14]. In a previous report, Kim et al. described two episodes of myocardial ischemia: the first one after eight hours and the second one about 24 hours later the beginning of 5-FU intravenous infusion and underlined that patients with a history of coronary artery disease have a significantly increased risk of 5-FU-induced cardiotoxicity [19]. Accordingly, our case report is the first one demonstrating a very late onset of ischemic symptoms after termination of 5-FU infusion. This observation may have important clinical implications about short-term follow up of these patients. Moreover, our case report shows that also patients without known coronary artery disease may develop 5-FU induced cardiotoxicity.

CONCLUSIONS

In conclusion, risk stratification of patients undergone to 5-FU administration alone or in combination with other chemotherapeutic agents is challenging and probably new trial are needed for detection patients' risk factors related to 5-FU side effects and/or cardiotoxicity in order to define better which patients may benefit from optimum anti-angina prophylaxis and careful close monitoring in this setting.

Disclosure statement

The authors did not report any potential conflict of interest.

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