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CASE REPORT

Acute heart failure after treatment with 5-fluorouracil

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Summary

Anthracycline cardiotoxicity is cumulative and can cause congestive heart failure. The cardiotoxicity caused by 5-fluorouracil (5-FU) is acute and is usually observed during the first cycle of chemotherapy. We present the case of a female patient operated on for colorectal cancer and receiving her first postoperative chemotherapy cycle. Three hours after the initiation of continuous 5-FU infusion she developed signs of acute heart failure (AHF) and pulmonary edema. The patient did not have any previous history of heart disease. Symptoms resolved 24 hours from the onset of the episode after the initiation of the relevant emergency therapy.

One of the most common symptoms related to 5-FU cardiotoxicity is chest pain. In case of such a toxicity treatment should be switched to another antineoplastic agent.

Key words: cardiotoxicity, chest pain, 5-fluorouracil

Introduction

One of the main causes of AHF in elderly patients is drug toxicity. The range of such drugs used currently in oncology is enormous. There are two groups: 1) anthracycline family: doxorubicin, epirubicin, daunorubicin, mitoxantrone are some of the most frequently used drugs with wide therapeutic range; 2) non-anthracycline agents: 5-FU, cyclophosphamide (high dose), vinca alkaloids, paclitaxel etc.

Cardiotoxicity could be a life-threatening condition, developing in a matter of hours. Anthracyclines and their cardiotoxicity are intensely researched. Anthracycline-derived cardiotoxicity is of cumulative type and presents with congestive heart failure. On the contrary, the cardiotoxicity caused by 5-FU is usually acute and occurs during the first cycle of chemotherapy as AHF [1].

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Case presentation

A 55-year-old female diagnosed with colon cancer, both endoscopically and histologically, was operated on. Hepatic metastases were also found during the operation. Initial surgery included right hemicolectomy with lymph nodes dissection. Histopathology confirmed moderately differentiated adenocarcinoma and regions of mucous production, and massive whole-thickness infiltration of the bowel wall. Two of the 6 excised lymph nodes were infiltrated by carcinoma (pT3N1M1, stage 4). Cholecystectomy and resection of the hepatic segments IVB and V was performed one month after the first surgical intervention.

One month after this second operation the patient was admitted for the first cycle of chemotherapy in relatively good clinical condition: normal cardiopulmonary function, no gastrointestinal complaints, without hepatomegaly or ascites on examination. Full blood count, PTT, fasting blood sugar, urea, creatinine, electrolytes, CPK, bilirubin, proteins and albumin

were normal, while hepatic enzymes were slightly elevated: ASAT 81 U/L (normal < 48), ALAT 44 U/L (normal < 44).

Chemotherapy included oxaliplatin 90 mg/m^2, 5-FU 2,400 mg/m^2, leucovorin 400 mg/m^2 (FOLFOX), ondansetron and metoclopramide. During 5-FU infusion she complained of nausea, headache and slight shortness of breath at rest, which were considered as side effects of chemotherapy. Three hours after the completion of infusion the patient started complaining of deterioration of shortness of breath and onset of chest pain. On examination she had heart rate of 150 bpm and blood pressure 110/65 mmHg, tachypnea, marked perioral cyanosis and was pale, cold and with sweaty skin. On auscultation, initially there were scarce fine rhonchi on both lung bases and 5 hours later large crackles appeared bilaterally. The cardiologic examination confirmed AHF with pulmonary edema. ECG demonstrated sinus tachycardia of 150 bpm and negative T waves in V3-V6 (Figure 1). Potassium level was normal (4.02 mmol/l), as were the acute myocardial enzymes (CPK, CPK-MB and troponin). Chest radiography implied pulmonary edema (Figure 2). Echocardiography diagnosed signs of left ventricle remodeling and hypoxia with severe pump dysfunction (IF=18%) and compromised filling of the right ventricle (restrictive type heart failure).



Figure 2. Bilateral pulmonary edema.

Treatment was initiated immediately and included furanthryl, morphine and i.v. nitrate. Lung auscultation

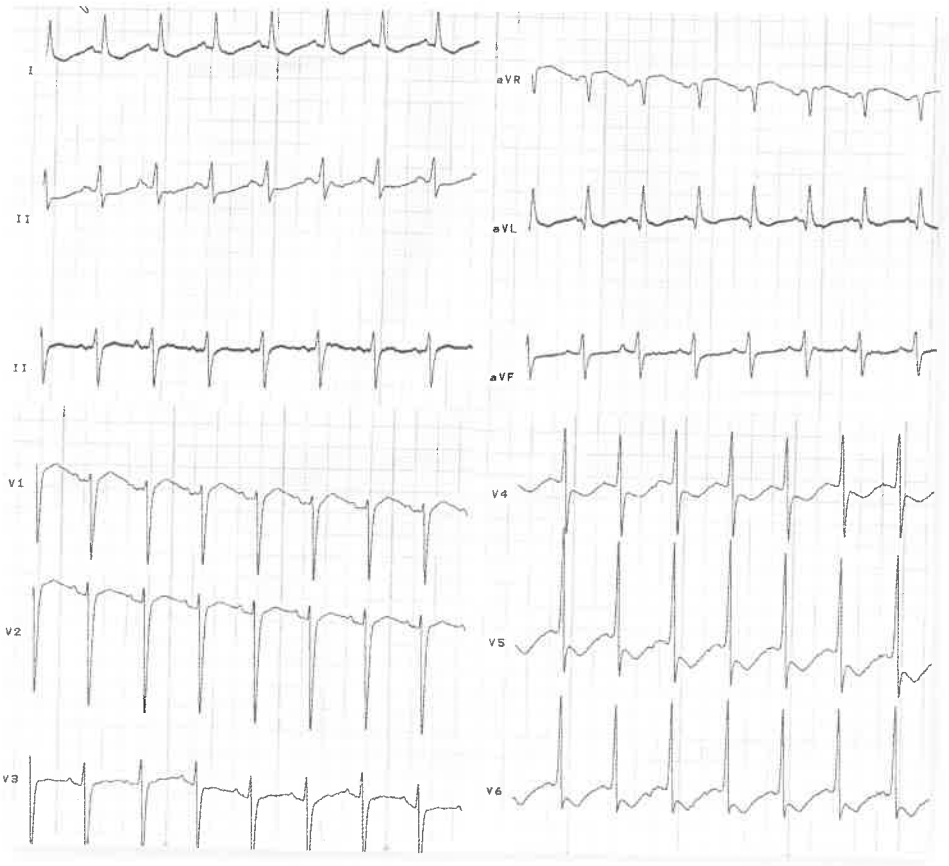


Figure 1. Sinus tachycardia and negative T wave in V3-V6.

findings improved significantly 4 hours later. Only some tachypnea and slightly decreased heart rate of 107-120 bpm persisted for longer, but without extrasystoles. Diuresis was 1200 ml/4 h. The pulmonary edema resolved completely 24 hours later. Dobutamin i.v. was also initiated due to the low output heart failure.

The patient was discharged later when her clinical condition improved and the signs of heart failure resolved completely. Therapy on discharge included diuretics, ACE inhibitor and trimetazidine. In the following 6-month period of follow-up the patient didn't have any signs of heart dysfunction or pulmonary edema.

Discussion

According to the relevant literature some of the most frequent adverse effects of 5-FU are diarrhea, nausea and vomiting, mucositis and bone marrow suppression [2]. While one of the side effects of continuous i.v. regimes of 5-FU is gastrointestinal mucositis, bolus regimes are notorious for causing bone marrow suppression with the lowest leukocyte level from days 7-14. Though extremely rare, there are also reports of neurotoxicity (5%) with signs of cerebral ataxia, dysarthria, nystagmus and diplopia [2].

The described case demonstrates one of the rarely observed but potentially life-threatening adverse effects of 5-FU therapy - cardiotoxicity. 5-FU is an antimetabolite which distributes in the body fluids by simple diffusion. It readily enters the cells where it is converted into active nucleotide forms. The pathophysiology of 5-FU cardiotoxicity is intensely researched nowadays. One of the main pathways of cardiotoxicity involves its metabolic product - fluoroacetate- which causes widespread myocardial hypoxia due to depletion of the levels of energetically charged ATP [3]. According to the latest research findings, 5-FU causes sharp increase of the oxygen consumption and dramatic alteration of the erythrocyte metabolism. The most important adverse effect is decrease of ATP. This causes permanent changes of the erythrocyte structures and function, proton pump blocking and increase of the membrane permeability. As a result, the myocardium suffers from lack of oxygen [4]. Myocardial histology after sudden death of patients treated with 5-FU demonstrates sarcoplasmatic proliferation and significant vacuolation. Similar morphological features of toxicity have been also observed after therapy with doxorubicin [5].

Cardiac complications of 5-FU therapy happen in 7.6% of all patients. The initial symptoms include chest pain, hypotension or hypertension, anxiety, dyspnea, arrhythmia or even sudden death [3]. 5-FU cardiotoxicity is acute and is observed most frequently on days 3-4 of continuous i.v. regimes. In patients on bolus regimes it develops usually during the 4th therapeutic cycle [3,6]. One of the most frequent symptoms related to 5-FU cardiotoxicity is chest pain [7]. There are also case reports of peripheral arteries or coronary spasms (Prinzmetal angina) [8-10] and cases of cardiac arrhythmias, dilatation of the heart due to cardiomyopathy, myocardial infarction and fatal cardiogenic shock [11]. Only 18% of the patients with signs of cardiotoxicity on 5-FU therapy have had previous history of heart disease [12].

The various toxic effects of 5-FU could be modulated if administered concomitantly with platinum compounds and leucovorin. The presented case is an example of increased toxicity.

The exact mechanism of 5-FU-induced cardiotoxicity is not completely understood. In most of the reported cases it has occurred during the first cycle and mostly at night [13]. These symptoms are reversible after the termination of 5-FU infusion and initiation of conventional hearth failure therapy.

The described case is a combination of clinical symptoms such as chest pain, ST–T wave elevation on ECG and AHF due to left ventricle dysfunction, while the acute myocardial enzymes were normal. The gradual improvement of the left ventricle function and its reversal in a matter of days after chemotherapy confirms the role of 5-FU in the development of cardiotoxicity.

We conclude that cardiotoxicity is an important but underestimated problem in 5-FU therapy, which can have negative effects on the patients' quality of life and survival. Immediate diagnosis of acute complications during therapy is required. The patients who are at significantly increased risk of cardiotoxicity are mostly those with previous hearth disease, high-dose regimes, electrolyte imbalance, prior mediastinal radiotherapy or other previous cardiotoxic therapy.

All patients need constant cardiac monitoring, especially during the first cycle. In any case of 5-FU cardiotoxicity therapy must be switched to another antineoplastic drug.

Medications for prophylaxis of cardiotoxicity include antioxidants, Ca channel blockers (only if normal myocardial function) and low-molecular-weight heparin [14].

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