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Acute Coronary Syndrome during Chemotherapy: Report of Three Cases

Síndrome Coronariana Aguda durante o Uso da Quimioterapia: Relato de Três Casos

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Abstract

Venous vascular events (VE) are frequently diagnosed during cancer chemotherapytreatment. The arterial VE are uncommon and can be lifethreatening if incorrectly diagnosed and treated. The authors describe three uncommon cases of acute coronary syndromes diagnosed during chemotherapy. Patient 1 had a germ cell tumor of testis and presented no risk factor for coronary diseases and was just 27 years old. However, he presented cardiac arrest and acute myocardial infarct in a post-mortem examination. Patient 2, with a lung adenocarcinome, ex-smoker and with family history of AMI, presented an acute myocardial infarct during the second cycle of gemcitabine and cisplatin regimen. Patient 3 had a squamous cell carcinoma of the right tonsil, was hypertensive, diabetic and exsmoker; however, he presented three major vascular events during chemotherapy with 5-fluorouracil and cisplatin. Cancer chemotherapy, especially when cisplatin is administered, may be uncommonly associated with coronary ischemic events.

Key words: Myocardial infarction; Antineoplastic Agents

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INTRODUCTION

Vascular events (VE), either venous or arterial, can be produced by cancer chemotherapy (CC). Arterial ischemia uncommonly occurs secondary to chemotherapy in coronary, cerebral and extremities vessels[1-3]. Basicaly, arterial ischemia can be related to vasospasm phenomenon or occurrence of thrombosis.

The classic CC agent related to acute coronary syndrome is 5-fluorouracil (5-FU), and the proposed mechanism is arterial vasospasm[4]. The wide spectrum of VE are known complications of cisplatin-based chemotherapy[5] .

CASE REPORTS

PATIENT 1

A 27-year-old man was treated with right orchidectomy and diagnosed with a testicular seminoma, stage IS (pT1N0M0S1) in March 2006. His past medical history was unremarkable. The unique cardiac risk factor was overweight. Four months later he presented disease recurrence in retroperitoneal and mesenteric lymph nodes and was submitted to BEP regimen of chemotherapy; i.e. bleomicin 30 U i.v. on days 2, 9 and 15, etoposide 100 mg/m^2 i.v. on days 1 to 5 and cisplatin 20 mg/m^2 i.v. on days 1 to 5, in a 3-week schedule.

On day 8 he was admitted in the Chemotherapy Center complaining of burning chest pain without radiation, nausea, and emesis that initiated 2 days before. Right after his admission, he suddenly became unresponsive and cardiorespiratory arrest was diagnosed. Despite cardiopulmonary resuscitation he died 40 minutes later. Cardiac enzymes collected before cardiac arrest were creatine kinase (CK): 456 U/L (normal: 55 to 170 U/L) and MB isoenzyme (MB-CK): 57 U/L (normal: <0.16 U/L). Necropsy examination diagnosed acute myocardial infarction (AMI) with recent thrombus on ulcerated plaque that occluded the right coronary artery. There was just a subjacent mild coronary atherosclerosis.

PATIENT 2

A 60-year-old man was diagnosed with left lung well-differentiated adenocarcinome, stage IV (cT4N3M1) with contra-lateral lung and bone metastasis, in June 2006. He had smoked 20 cigarettes a day for 42 years and dbeen an ex-smoker for two years. His brother had AMI at the age of 45 . The patient was submitted to a palliative chemotherapy with gemcitabine i.v. 1000 mg/m^2 on days 1 and 8 and cisplatin i.v. 80 mg/m^2 on day 1, in a 3-week regimen.

On day 8 of the third cycle of chemotherapy, the patient was admitted in the Emergency Department (ED) with burning precordial pain with upper left arm radiation for two hours. Initial electrocardiogram (ECG), obtained during chest pain, showed mild ST-segment elevation in leads DII, DIII, and aVF (Fig. 1A). The pain was completely relieved with 5 mg sublingual isosorbide dinitrate. Subsequent ECG turned normal (Fig. 1B). Cardiac enzymes increased with a peak troponin I of 3.17 ug/L (normal: <0.16 ug/L). The patient was treated with aspirin, clopidogrel, and low molecular weight heparin. After coronary angiography that showed normal coronary arteries, oral diltiazem was initiated.

Because of important VE possibly related to CC, the chemotherapy regimen was changed to carboplatin i.v. area under the curve (AUC) of 5 on day 1 and paclitaxel 175 mg/m^2 i.v. on day 1, in a 3-weel schedule. On day 2 of the newer treatment, the patient presented a burning chest pain again which was relieved after sublingual isosorbide dinitrate. After this second event, the treatment was changed (for the second time) to etoposide 100 mg orally on days 1 to 7, in a 3-week schedule.

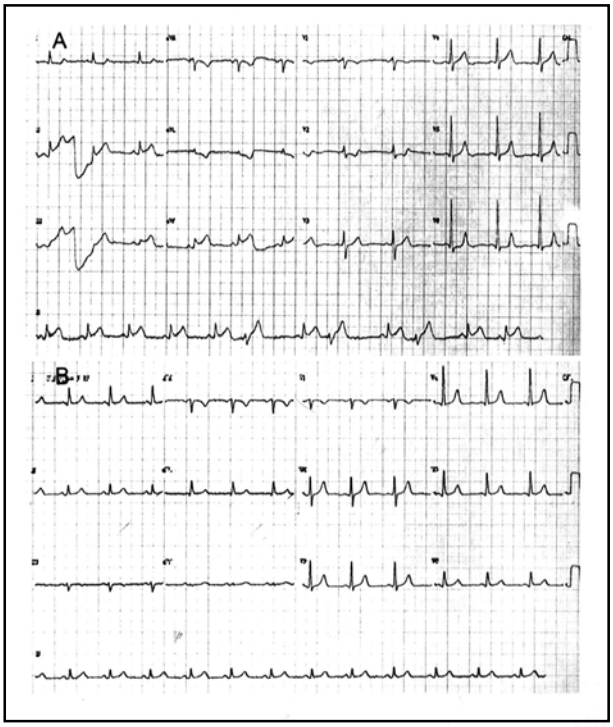

Figure 1. A- Initial ECG at the time of chest pain and before sublingual isosorbide dinitrate showing ST-segment elevation in leads DII, DIII, and aVF with ST-depression in aVL and V2. B- ECG taken after sublingual isosorbide dinitrate without relevant findings

Patient 3

A 56 year-old man was diagnosed in January 2006 with a poorly differentiated squamous cell carcinoma of the right tonsil, stage IVB (cT2N3M0). Past medical history included hypertension and diabetes. He had smoked 20 cigarettes a day for 30 years and had been an ex-smoker for two years. The patient was submitted to treatment with 5-FU i.v. 1000 mg/m^2 on days 1 to 5 and cisplatin i.v. 100 mg/m^2 on day 1, in a four-week schedule. On day 8 of the first cycle, he was admitted in the ED with nausea, diaphoresis, dyspnea, and precordial oppressive pain over six hours. ECG showed no notable changes, but cardiac enzymes elevation diagnosed non-Q-wave AMI. The CK, MB-CK, and troponin I levels were elevated after 6, 12, and 26 hours after admission, respectively: CK 119, 89, 55 U/L; MB-CK 35, 17, 11 U/L; and troponin I 0.97, 0.65, 0,84 ug/L. Treatment with clopidrogrel, aspirin, and intravenous heparin was initiated. The coronary angiography showed complete obstruction of the distal third of the posterior descending coronary artery.

The cardiac rhythm was normal and no complication during coronary angiography was observed, but two days later (on day 10 of the chemotherapy), he presented diffuse abdominal pain, tachycardia, diaphoresis, hypotension and abdominal distension. Exploratory laparotomy diagnosed superior mesenteric ischemia and the patient was submitted to segment intestinal resection. On the same day he was diagnosed with acute ischemia of right lower limb immediately treated with a Fogarty embolectomy. Currently, he is being treated with palliative weekly methotrexate i.v. 30 mg/m^2 and has no cardiac symptoms.

DISCUSSION

AMI and myocardial ischemia (MI) has been reported to occur in association with some CC, especially 5-FU, cisplatin, vinca alkaloids and BEP regimen (bleomicin, etoposide and cisplatin) for germ cell tumors[3,4,6]. Using the PubMed database and the key words "acute coronary syndrome" or "myocardial infarction" or "coronary spasm" and "cancer therapy" or "cancer chemotherapy" we found 35 abstracts of case reports (describing 49 patients) in English literature. The majority of the reports described patients submitted to cisplatin-based (24 patients), 5-FU (11 patients) or capecitabine (8 patients) treatment.

Numico *et al*. studied prospectively 108 stage III and IV non-small cell lung cancer submitted to chemotherapy treatment with gemcitabine and cisplatin, and documented two cases of AMI[1]. In our report, patient 2 was treated with gemcitabine and cisplatin regimen and diagnosed with AMI, probably secondary to coronary vasospasm, because of coronary angiography without vessels obstructions. Few reports of vasospastic angina and AMI secondary to vasospasm when using cisplatin and gemcitabine have been published[7,8] .

When patient 2 was rechallenged with other drugs (paclitaxel and carboplatin), he presented angina pectoris again. Chasen et al. described a patient with coronary vasospasm associated with carboplatin, and Nquyen-Ho *et al*. a case of AMI probably caused by coronary vasospasm secondary to paclitaxel treatment[9,10]. To the best of our knowledge this is the first report of two different chemotherapy regimens eliciting acute coronary events in the same patient.

Unfortunately, no large prospective study has been conducted aiming to analyze the real incidence of acute coronary events in overall cancer patients submitted to different types of chemotherapy. The general frequency is expected to be very small. Two recently published prospective studies investigated chemotherapy-induced cardiovascular changes in patients with testicular cancer that used the BEP regimen. Two patients (2/244, 0,8%) presented AMI considering all the patients followed in the studies[3,6]. In our report patient 1 was submitted to BEP regimen and necropsy documented AMI with thrombus in right coronary. It is important to note that AMI can occur even in young patients without known cardiovascular risk factors.

Cisplatin is a known CC related to thrombosis[5]. The proposed mechanisms to this phenomenon are direct endovascular damage; decreased activity of anticoagulant protein C; elevated plasma vWf level and hypomagnesemia[2]. Patient 3 had been submitted to cisplatin and continuous 5-FU and presented three important vascular events, i.e.: AMI, mesenteric ischemia and lower limb acute ischemia.

Although it is difficult to define the cause of the VE in our patients, the timing of its appearance suggested a relation with the administration of chemotherapy. Patient 1 was overweight, but too much young to be considered in risk for an AMI. According to our impressions, the necropsy showed just mild atherosclerotic changes in addition to the thrombus in right coronary artery. Patient 2 was a 60 year-old man, heavy ex-smoker, with a documented AMI with normal coronaries in coronariographic study. In this case the vasospastic nature of the lesion is more probable. Patient 3 had important known risk factors for the occurrence of arterial VE. He was ex-smoker, diabetic, and hypertensive, but the occurrence of three major VE on day 8 of chemotherapy suggests at least a co-participation of the CC in the genesis of the VE.

The use of cardiotoxic CC agents should be spared in patients with known coronary disease. They can be used in special situations after considering the risk versus benefit rationale and taking patient's consent. The use of cardiotoxic CC agents in patients with established cardiovascular risk factors (but without coronary artery disease) is more challenging. To the best of our knowledge, no published guideline addressed this approach. A routine cardiologic consultation before initiating cardiotoxic chemotherapy is suggested, especially when using fluoropyrimidines or cisplatin-based regimens. Dynamic investigations using stress tests (exercise ECG, dipyridamole-thallium scintigraphy, or dobutamine echocardiography) before the beginning of CC may be important especially in high-risky patients. It is suggested a tight clinical monitoring of all patients receiving CC with agents reported to have been associated with acute coronary events. Patients should be immediately informed about the symptoms and the condition recognized and managed.

CONCLUSION

Attemtion should be paid that acute coronary syndrome may be an important complication of CC, especially with cisplatin-based regimens, even in the absence of overt risk factors for coronary artery disease.

Conflicts of interests: nothing to declare.

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Resumo

Eventos vasculares (EV) venosos são frequentes durante o tratamento quimioterápico. Os EV arteriais são incomuns e podem ser graves se não diagnosticados e tratados corretamente. Os autores descrevem três casos incomuns de síndromes coronarianas agudas diagnosticadas durante a quimioterapia. O paciente 1, com tumor de células germinativas de testículo, não apresentava nenhum fator de risco para doença coronariana e tinha apenas 27 anos, no entanto, apresentou uma parada cardiorrespiratória com diagnóstico *post-mortem* de infarto agudo do miocárdio (IAM). O paciente 2, com adenocarcinoma de pulmão, era ex-tabagista, apresentava uma história familiar de coronariopatia e apresentou um IAM durante o segundo ciclo de gencitabina e cisplatina. O paciente 3, com diagnóstico de carcinoma de células escamosas de tonsila palatina direita, apresentou três eventos vasculares maiores durante o tratamento com 5-fluorouracil e cisplatina. Era hipertenso, diabético e ex-tabagista. A quimioterapia, especialmente quando utilizada a cisplatina, pode estar relacionada com eventos coronarianos agudos.

Palavras-chave: Infarto do miocárdio; Antineoplásicos