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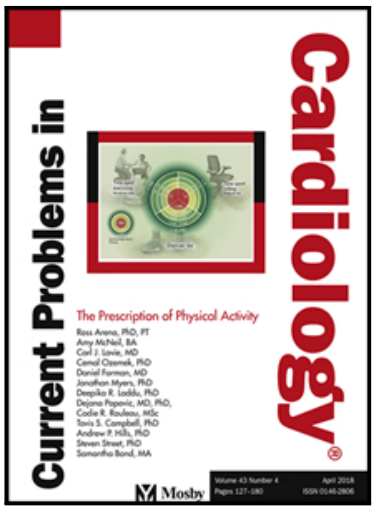

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AC-MODE OF CHEMOTHERAPY AS A TRIGER OF CARDIAC SYNDROME X: A CASE STUDY

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- Abstract

In the period of dynamic development of pharmacological possibilities in the modern oncology, unfortunately, the issue of cardiotoxicity of chemotherapy did not lost its urgent value. Cardiotoxicity implies structural and functional myocardial alteration, together with an increase in the concentration of highly sensitive markers of myocardial necrosis, in particular T and I troponins, and N-terminal pro-BNP, as well as with a subclinical or clinical decrease in the LVEF. It is noteworthy that cardiotoxicity is manifested not only by the development of anthracycline cardiomyopathy with a high risk of convention into heart failure. It also can cause various cardiovascular pathologies, in particular cardiac syndrome X. This study described chemotherapy-induced microvascular angina in 23-year-old otherwise heathy woman. The diagnosis is challenging for doctors, since microvascular flow may be only detected by using functional test.

Keywords

cardiotoxicity, chemotherapy, cardio-oncology, myocardial metabolism

- Introduction

In the period of dynamic development of pharmacological possibilities in modern oncology, unfortunately, the cardiotoxicity of chemotherapy did not lose its urgent value[1]. Cardiotoxicity implies structural and functional myocardial alteration, together with an increase in the concentration of highly sensitive markers of myocardial necrosis, in particular T and I troponins and N-terminal pro-BNP, as well as with a subclinical or clinical decrease in the LVEF[2]. It is noteworthy that cardiotoxicity is manifested not only by developing anthracycline cardiomyopathy with a high risk of the convention into heart failure[3]. It also can cause various cardiovascular events, in particular cardiac syndrome X. In this respect, presenting a given clinical case demonstrates microvascular angina in 23-year-old female patient with breast cancer associated with AC mode (doxorubicin (adrymiacin) + cyclophosphamide) of chemotherapy intake.

- ***Case report***

A 23-year-old female patient, height 167 cm, weight 59 kg, menarche at the 12-year-old, adherent to a healthy lifestyle, nonsmoker, married, with 2 pregnancies, unemployed, not using

hormonal contraceptives, referred to the cardiological department for exercise-induced severe chest discomfort, radiating into the interscapular region, the left shoulder and the left forearm. According to medical history, she had breast cancer (left breast cancer developed from glandular epithelium: T1N0M0G1, non-luminal type, Her2/neu positive 1+). She underwent a mastectomy and following 5 adjuvant courses of chemotherapy in AC mode (doxorubicin+cyclophosphamide). The time interval between courses was 21 days, no cardiovascular drugs patient received. Doxorubicin's cumulative dose was 450 mg/m^2.

In particular, before and during chemotherapy and directly after the last course, ECG and Echocardiography were carried out and no abnormalities were found. Notably, she had taken nitroglycerin spray since the first days of chest pain, after which a considerable worsening of symptoms was observed.

Medical life history data: she had no heart complain before seeking the doctor. Pain occurs spontaneously with different intensity and duration. No surgery. She denies having TB, HIV, HepB and HepC. No gynecological disorders.

Inspection: moderate-severity condition, the skin – yellow-beige, the mucous membranes – pinkish and moist, no rash is seen.

No pathology was observed during palpation, percussion of the abdomen.

Heart rate 74 beats/min, BP 120/75 mm Hg, O2 saturation – 99 %.

The patient underwent all mandatory laboratory examinations and imaging tests. According to ECG, echocardiography, and CXR, no changes were identified. No abnormalities were revealed in routine blood analysis, urinalysis, blood biochemistry. Plasma glucose level, HbA1C, CRP, adrenalin, noradrenalin, estrogen levels did not demonstrate deviations from the referent values. PCR examination of CMV, HSV, HBV, HCV and HIV test were negative. Markers of myocardial necrosis (Troponin I, LDH and CK-MB), NT-pro-BNP and ST-2 level were normal. Thyroid profile also was normal.

Treadmill test yield positive results. Due to the positive treadmill test, absence of deviation in the laboratory tests and instrumental examinations, and presence of typical angina, coronary angiography was performed. During the examination, pathological changes in the great epicardial arteries were not observed; in this respect, microvascular angina was admitted. Intracoronary acetylcholine provocation test was conducted, the result of which was positive. Biochemical assays of the blood sample taken from the coronary sinus zone during the ischemic period showed an

increased level of lactate. During myocardial TI-201 stress scintigraphy, ischemic damage was visualized. During the cardiac stress test, reduced LVEF was values.

Based upon the clinical and paraclinical data (young adult, absence of cardiological risk factors, especially systemic hypertension and DM), structural and functional safety of heart chambers, absence of ECG and echocardiographic signs of IHD, and also regular menstrual cycle, normal catecholamines level, positive acetylcholine, and stress test, an increased level of lactate, the patient was diagnosed "Microvascular angina".

Due to the absence of organic cause for the disease, a psychologist consultation was organized, whose opinion certified that the patient is practically healthy, stress-resistant, with low anxiety level. During the examination, phobic and depressive disorders were excluded.

Metoprolol (50.0 mg twice per day), Lisinopril (5.0 mg once per day) and trimetazidine (80.0 mg once per day) were prescribed and also recommended to keep a balanced diet and healthy lifestyle, including cardiorespiratory fitness and vitamin complex CardioActiv intake, which includes coenzyme Q10, and B group vitamins (once per day).

During the follow-up visits to the cardiologist, the patient remains without complications and pathological conditions according to data obtained from laboratory analysis and instrumental examinations.

- ***Discussion***

Regarding the young age, absence of CVD and comorbid pathology in medical history, we state that the fact of chemotherapy should be considered a leading factor of cardiovascular homeostasis destabilization. In this regard, the onset of microvascular angina is associated with chemotherapy. Analyzing the molecular mechanisms of doxorubicin and cyclophosphamide-induced cardiotoxicity, it is worth noting the latter's role in the intensification of lipid peroxidation (LPO)-mediated cardiovascular disturbances[4]. In particular, the development of mitochondrial dysfunction and, as an outcome, the energy inconsistency of cardiomyocytes leads to functional myocardial disequilibrium up to HF development of and even myocardial onecrosis.[5] Moreover, it is also worth distinguishing the LPO-independent processes, particularly the expressive activity of topoisomerase, neuregulin protein-1 destabilization, and the disruption of the iron transport systems. It is noteworthy that in this particular case, endothelial damage with the development of ED is noted, which is the pathological orchestrator for atherosclerosis, AH, AF, and other CV events.[6]

There is also an interesting key point of chemotherapy, especially doxorubicin-induced cardiotoxicity – sirtuins.[7] Mitochondrial sirtuins reduce the degree of myocardial ischemia-reperfusion injury, expansion of cardiac hypertrophy, and heart failure.[8] Therefore, elevation in cardiac tissue levels of sirtuins for improvement of myocardial mitochondrial energetics is a novel approach in several cardiac disorders. Sirtuins are activated by low energy levels and stimulate energy production by activating transcription factors and enzymatic regulators of cardiac energy metabolism.[9] Moreover, DOX interferes with myocardial energetics; thus, a hopeful approach to reduce the cardiotoxic effects of DOX may be to target mitochondria and improve metabolic function[10]. SIRT3 overexpression protects cardiomyocytes from DOX-induced mitochondrial damage through the prevention of mitochondrial destruction and cellular death in the heart.[10]

Moreover, doxorubicin-damaged endothelial cells can trigger the development and progression of cardiomyopathy by decreasing the release and activity of key endothelial factors and inducing endothelial cell death.[11] Thus, the endothelium represents a novel target for improving the detection, management, and prevention of doxorubicin-induced cardiomyopathy.[12] Because of the key role of microvasculopathy in cardiac syndrome X, doxorubicin-induced endothelial cells damage is a key mechanism for microvascular angina development in a young patient without any risk factors or comorbid pathology.

The anti-remodeling and cardioprotective properties of prescribed drugs are also noteworthy in addition to some antioxidant properties of β-adrenoblockers. β-adrenoblocker and ACE inhibitor were prescribed in lieu of the recommendation for both the management of patients with chemotherapy-related myocardial dysfunction and for the treatment of patients with coronary X syndrome.[13] Trimetazidine and Cardio-Active were used as a stabilizer of defective intramyocardial metabolism and as a limitation of LPO-associated damage of heart tissue.[14-16]

- Conclusion

We describe a case of a patient undergoing chemotherapy for a breast cancer in which microvascular angina occurs in acute phase of oncologic treatment. Further longitudinal studies are needed to assess the incidence of microvascular angina in oncologic patients. In this context, besides modification of prescribed medication, it is essential and economically practical to form national registers of cardiooncological patients, design manuals with the patients' curation protocols adapted to chemotherapy modes, and creation of schools for such patients.

Declaration of Competing Interest

all authors carefully read and approved the final version of submission without any potential conflict of interest

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