Srce i krvni sudovi 2023; 42(2): 46-49

Case report

The significance of long-term patients monitoring after anthracycline administration

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Abstract Anthracyclines are drugs used to treat various types of cancers, including breast cancer. They are still among the most effective anticancer drugs used today and their broad use has dramatically improved cancer survival statistics. Unfortunately, though mortality rates decrease with their use, life-altering cardiac sequelae from anthracyclines remain a problem, such as patients developing late-onset heart failure secondary to anthracycline-induced cardiotoxicity (AIC). We present a case of 63-year-old female who was admitted to the Cardiology Clinic due to the symptoms of heart failure. Fourteen years earlier she had a left-sided mastectomy due to breast cancer treated with radiotherapy and chemotherapy. The chemotherapy regime was FAC (5-fluorouracil, doxorubicin and cyclophosphamide). Echocardiogram showed enlarged left ventricle (58mm/51mm), with reduced ejection fraction (EF 20%). There was a large effusion in the left pleura. This finding was primarily related to the treatment of breast cancer with chemotherapy.

Kew words anthracycline-induced cardiotoxicity, breast cancer, heart failure

Introduction

Anthracyclines are drugs extracted from Streptomyces spp. and used to treat various types of cancers, including leukemia, lymphoma, breast cancer and many metastatic cancers[1]. Even though anthracyclines were discovered over 50 years ago, they are still among the most effective anticancer drugs used today[2]. The different types available for treatment are: Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Valrubicin. The explanations of cytostatic and cytotoxic actions of anthracyclines point to a number of different mechanisms, including free radical formation, lipid peroxidation, direct membrane effects and enzyme interactions. The most widely accepted mechanism for the action of anthracyclines is their interaction with topoisomerase-II. The ternary complex thus formed prevents the re-ligation of the ds-DNA breaks. Subsequently, it promotes growth arrest and apoptotic cell death[1,3].

The broad use of anthracyclines for over 40 years has dramatically improved cancer survival statistics. Unfortunately, though mortality rates decrease with anthracyclines, life-altering cardiac sequelae from anthracyclines remain a problem, with a range of 5% to 23% of patients developing late-onset heart failure secondary to anthracycline-induced cardiotoxicity (AIC)[4,5].

Anthracycline-mediated cardiotoxicity is dose-dependent and cumulative, with the damage imposed to heart occurring upon the very first dose and then accumulating with each anthracycline cycle. Cardiotoxic effects of anthracyclines range in severity and are classified by time of onset as *acute*, occurring during or immediately after infusion; *early*, occurring within 1 year of exposure; and *late*, occurring 1 to 20 years after initial exposure[5,6].

Case presentation

We present a case of 63-year-old female who was admitted to the Cardiology Clinic due to the symptoms of heart failure. Patient complained of increased fatigue, which has been present for the past three months. She was initially treated at a regional hospital, when bilateral pleural effusions were found (larger on the left side) and dilated cardiomyopathy with ejection fraction (EF) 25% was found by echocardiography. Pleural biopsy puncture was performed and no significant changes were found. A CT (computerized tomography) of the thorax was performed, which showcased consolidation of pulmonary parenchyma and severe fibrotic changes in basal segments of the both lungs. Diuretics, beta-blocker and amiodarone were introduced into the therapy, but the day before admission to our Clinic, she complaint of shortness of breath, which is why she was rehospitalized. She had a positive family history for cardiovascular diseases (CVD).

Fourteen years earlier, she had a left-sided mastectomy due to breast cancer treated with radiotherapy and chemotherapy. The chemotherapy regime was FAC, which consisted of 5-fluorouracil, doxorubicin and cyclophosphamide. Two years after mastectomy, the reconstruction of the left breast was performed (regularly monitored, tumour markers were normal).

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Physical examination showed regular heart rate, with discrete systolic murmur over the apex, heart rate was 110 bpm, and arterial blood pressure was 100/70 mmHg. Auscultatory over the lungs left base weakened respiratory sound. Electrocardiogram (ECG) showed sinus rhythm with left bundle branch block (LBBB). Laboratory tests showed increased B-type natriuretic peptide (BNP) 613, C-reactive protein was 28.7, troponin 0.0049, D-dimer 3.69, iron 4.0, with preserved renal function.

X-ray heart and lungs showed: no active pathological changes were seen in the lung parenchyma. The right costophrenic sinus was shallower, while in the left the pleural effusion was present. The breast implant was observed on the left side. The cardiac silhouette was slightly enlarged. Echocardiogram (exam was hindered by the silicone implant in the left breast) showed enlarged left ventricle (EDD 58 mm, ESD 51 mm), with reduced ejection fraction (EF 20%) and without segmental kinetics changes. There was 2+ mitral regurgitation and 2+ tricuspid regurgitation, SPDK was 60 mmHg. This finding was primarily related to the treatment of breast cancer with chemotherapy. Color doppler sonography (CDS) of the right leg veins: without signs of thrombosis were the common femoral and superficialis veins, and popliteal vein. Soleal sinus was with organized thrombotic masses. Prolongation of anticoagulant therapy with elastic compression stockings was indicated for the next six months.

Due to the findings of persistent pleural effusion, deep vein thrombosis and history of malignant disease, an oncologist was consulted, who suggested that a chest CT should be performed, in order to rule out a relapse of the oncological disease. However, the patient was not motivated. A pulmonologist was also consulted, who did not indicate an urgent pleural puncture, but recommended a bronchoscopy, for which the patient was also not motivated. CT coronary angiography was performed which did not show angiographically significant narrowings.

During hospitalization, the patient had no anginal complaints, there was no change in objective findings, and serial ECGs did not register any new changes, as well as rhythm and conduction disorders. Auscultatory findings indicating that left pleural effusion persisted. She was discharged with beta-blocker, loop diuretic, potassium-sparing diuretic, direct-acting oral anticoagulant (DOAC) and proton pump inhibitor. Eventhough our patient was highly recommended to visit a cardiologist during initial cancer treatment and after, she wasn't motivated.

Discussion

Breast cancer is the most common cancer among women. In the last twenty years early diagnosis, neoadjuvant and adjuvant systemic treatment that targeted to specific molecular targets have significantly reduced the mortality from breast cancer[7,8]. However, the increase in survival has allowed us to observe the cardiotoxic effects of anticancer therapy and increased mortality from cardiovascular causes. Anthracyclines are among the most commonly used and effective drugs in breast cancer treatment. In the past 30 years, they have become an important component of adjunctive and palliative therapy for breast cancer[9].

As previously stated in the introduction AIC is a significat side-effect of medication. In a 2013 meta-analysis, clinical cardiac toxic effects were reported in 6% of patients treated with an anthracycline after a median follow-up of 9 years, and subclinical cardiac toxic effects were described in 18% of patients[10]. Manifestations of AIC can range from asymptomatic electrocardiogram (ECG) changes and left ventricular (LV) dysfunction to profound cardiomyopathy and end-stage heart failure (HF)[11]. Particularly in our patient, ECG showcased LBBB while echocardiography revealed left ventricular dysfunction. Increasing recognition of the significant morbidity and mortality associated with AIC has led to exploration of treatment modalities to prevent its development. In preclinical studies, significant acute cardiotoxicity occurs at the time of the initial administration of anthracyclines that starts a cascade leading to the eventual development of LV dysfunction and HF. The mechanism of anthracycline's early cardiotoxicity is known to be related to free radical injury, contributing to the formation of reactive oxygen species and leading to the apoptosis of cardiomyocyte and intracellular damage[12]. On the other hand, the mechanism of delayed cardiotoxicity in the long-term survivors is multifactorial including myocardial mitochondria related apoptosis which results in metabolic remodelling of heart[13]. However, delayed cardiotoxicity presents as overt clinical manifestations such as HF only in extreme cases, and only slowly progressing ventricular abnormalities are detected in many cases[13].

Despite efforts to detect early cardiac dysfunction in anthracycline-treated patients, many will experience symptomatic and asymptomatic HF. Cancer survivors who develop late AIC with New York Heart Association (NYHA) class III–IV heart failure have a poor prognosis, with a 1-year mortality of 40% and 2-year mortality of 60%[14].

Based on *The American Society of Clinical Oncology Clinical Practice Guideline* it is widely recommended that cardiovascular risk factors are assessed prior to the initiation of any anticancer therapy. That includes blood pressure, smoking habits, blood sugar, lipid levels, and electrolyte abnormalities[15,16,17,18]. In patients considered to be at high risk of adverse cardiac events (i.e., those with cardiovascular risk factors, previous or pre-existing cardiac disease, or abnormal baseline cardiac assessments or biomarkers, of older age, or who have received prior radiotherapy or anthracycline therapy), cardioprotective treatments should be considered, including ACE inhibitors, angiotensin receptor blockers, or beta-blockers, prior to initiation of anticancer therapy[15,18]. Regular cardiac monitoring should also be considered and discussed with patients deemed at high risk of adverse cardiac events. Recommended by *The European Society for Medical Oncology Clinical Practice Guidelines* echocardiography is the preferred method for cardiac evaluation (including LVEF) before, during, and after cancer therapy. Because of its availability, avoidance in radiation exposure and safety for patients with concomitant renal disease[19]. Pre-treatment cancer therapy-related cardiovascular toxicity (CTR-CVT)

risk assessment should be performed using a recognized risk stratification method where multiple risk factors are incorporated to determine patient-specific risk[20]. While further validation is needed, *Heart Failure Association-International Cardio-Oncology Society* (HFA-ICOS) risk assessment tools should be considered to determine pretreatment risk of CTR-CVT as they are easy to use and implement in oncology services[21].

Serum cardiac biomarkers, such as troponins and natriuretic peptides, are recommended in conjunction with routine diagnostic cardiac imaging, in the monitoring of patients with clinical signs and symptoms of cardiac effects[22].

Discontinuation of anthracycline chemotherapy is recommended in patients with cancer who develop severe symptomatic cancer therapy related cardiac dysfunction (CTRCD)[23]. Temporary interruption of anthracycline chemotherapy is recommended in patients who develop moderate symptomatic CTRCD, and in patients who develop moderate or severe asymptomatic CTRCD. Guideline-based HF therapy is recommended in patients who develop symptomatic CTRCD or asymptomatic moderate or severe CTRCD during anthracycline chemotherapy. The use of an ACE-I/ARB or angiotensin receptor–neprilysin inhibitor, a beta-blocker, a sodium–glucose co-transporter-2 inhibitor, and a mineralocorticoid receptor antagonist is recommended unless the drugs are contraindicated or not tolerated.

Considering the previous amnestic and physical examination that excluded other causes of heart failure, we can assume that our patient experienced anthracycline-induced cardiotoxicity. Taking into account previously mentioned guidelines and our case report, we see the importance of long-term follow-up of patients and the appropriate introduction of cardio-protective therapy.

Conclusion

Today we know that the usage of anthracyclines can have a significant cardiotoxic effects. Considering that, the administration of anthracycline in chemotherapy should be in agreement with the chosen cardiologist. Also, long-term monitoring of patients should be necessary, bearing in mind that it represents the most important form of prevention for AIC. Even thought the increased attention in this field, many questions have not yet been answered and new studies are needed.

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Sažetak

Značaj dugoročnog praćenja pacijenata nakon primene antraciklina

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Antraciklini predstavljaju grupu lekova koja se koristi za lečenje različitih vrsta karcinoma, uključujući karcinom dojke. Među najefikasnijim su lekovima koji se danas koriste i njihova široka upotreba dramatično je poboljšala statistiku preživljavanja od karcinoma. Nažalost, iako se stope mortaliteta obolelih od raka smanjuju njihovom upotrebom, određeni broj pacijenata koji su na terapiji antraciklinima razvija simptome i znake srčanog popuštanja usled kardiotoksičnosti prouzrokovane antraciklinima. Predstavljamo slučaj 63-godišnje žene koja je primljena u Kliniku za kardiologiju zbog simptoma i znakova srčanog popuštanja. Četrnaest godina ranije imala je levostranu mastektomiju zbog karcinoma dojke, nakon čega je lečena radioterapijom i hemioterapijom. Režim hemioterapije bio je FAC (5-fluorouracil, doksorubicin i ciklofosfamid). Učinjenim ehokardiografskim pregledom uočena je uvećana leva komora (58mm/51mm), sa smanjenom ejekcionom frakcijom (EF 20%). Uočen je veliki izliv u levoj pleuri. Ovaj nalaz prvenstveno je doveden u vezu sa lečenjem karcinoma dojke hemioterapijom.

***Ključne reči**: antraciklinima-prouzrokovana kardiotoksičnost, karcinom dojke, srčano popuštanje*