Case Report

Chemotherapy Related Severe Cardiac Dysfunction – Case Report

DIANA-ALEXANDRA CHERATA[1], DOINA CÂRSTEA[2], MIRELA ZAHARIE[2], C. BĂTĂIOSU[3], D. LUNGULESCU[4]

[1]*Departament of Cardiology, "Filantropia" Municipal Hospital, Craiova, Romania, PhD student*
[2]*Departament of Cardiology, "Filantropia" Municipal Hospital, Craiova, Romania*
[3]*Departament of Cardiology, Emergency County Hospital, Craiova, Romania*
[4]*Oncolab, Oncology Medical Center*

ABSTRACT: Cardiotoxicity is the most important side effect of cancer therapy resulting in increased patient morbidity and mortality, therefore understanding its occurrence mechanism and a correct and early diagnosis are essential for patients at risk of irreversible heart failure. We present the case of a patient who developed cancer therapeutics-related cardiac dysfunction, emphasizing the importance of regular echocardiographic evaluation for early detection of subclinical cardiac dysfunction and further cardiac monitoring. More sensitive parameters should be used to predict cardiotoxicity because the probability of cardiac function recovery diminishes in time, despite optimal heart failure treatment.

KEYWORDS: *chemotherapy, cardiotoxicity, cardiomyopathy, echocardiography*

Introduction

Over the last decade, national and international cardiology and oncology congresses have at least one session dedicated to cardio-oncology as a result of anticancer therapies development, that has led to an increased life expectancy of cancer patients, treatment-related comorbidities being a frequent matter.

Cardiotoxicity expressed through cardiac and vascular symptoms is one of the most alarming side effect of chemotherapy and radiotherapy. Cardiac dysfunction may be initially quiet-however severe and irreversible- has a negative effect on long-term survival and limiting future antineoplastic treatment options is an important matter. Therefore early detection and accurate cardiac function assessment is essential for early preventive therapeutic measures.

We present the case of a female patient who developed cancer therapeutics-related cardiac dysfunction, reflecting the importance of cardiac monitoring during cancer treatment.

Case Report

In 2010, a 54 year old woman was diagnosed and treated for stage II left sided breast cancer. Four years later, pulmonary metastases were detected and a new chemotherapy course was initiated. In October 2014, after she completed the last chemotherapy cycle, she begun to complain for acute shortness of breath and severe fatigue.

Initial treatment included left mamar sectorectomy, and axillary node dissection. Subsequently, she underwent 4 cycles of epirubicin (240 mg/m^2 total dose), cyclophosphamide (2.400 mg/m^2) and whole breast radiation with axillary boost (total dose of 50 Grays). As the tumor was established to be estrogen receptor positive, her subsequent medical regime consisted in hormonal therapy with tamoxifen over the next 5 years.

4 years later, a new chemotherapy course was initiated. Echocardiographic evaluation at that time (January 2014) showed normal cardiac function, normal left ventricle (LV) walls contraction and normal valves aspect, left ventricular ejection fraction (LVEF) of 60% and normal electrocardiogram (ECG). (Fig.1 A).

From January to August 2014, two cycles of TAC (docetaxel-167mg/m^2, doxorubicin-70 mg/m^2 and cyclophosphamide-1600 mg/m^2), 2 cycles of AC (doxorubicin 70 mg/m^2 and cyclophosphamide-1600 mg/m^2) and 4 cycles of FEC (5-fluorouracil-6970 mg/m^2, epirubicin-488 mg/m^{2}and cyclophosphamide-3.270 mg/m^2) were administrated. The patient did not show any clinical symptoms of heart failure during chemotherapy.

The patient had no smoking history, normal blood pressure values, normal weight, no history of diabetes, no personal or family history of cardiovascular diseases. She had been known with asthma for 28 years, treated with salmeterol and fluticasone propionate inhalor.

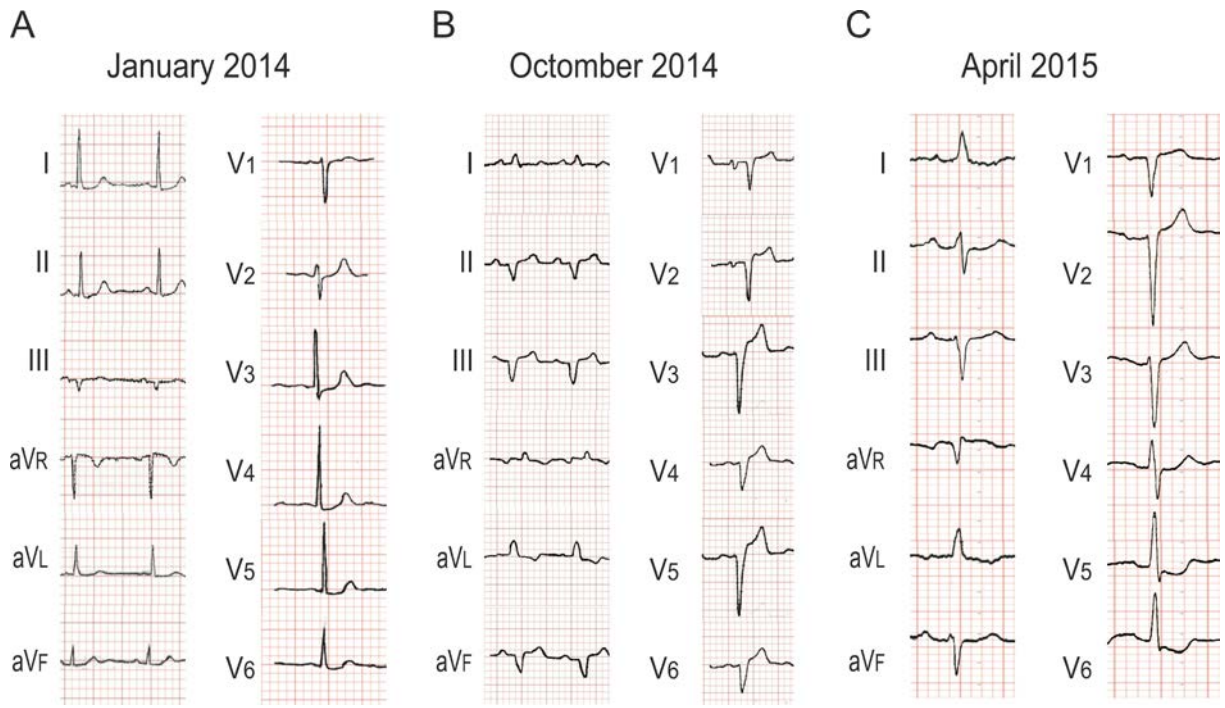

Fig.1. Electrocardiograms: A-before chemotherapy (January 2014), B - at the time of hospital admission (October, 2014), and C - 6 months later (April, 2015). A-sinus rhythm with 73 beats/min, QRS axis at 0^0 .B-sinus rhythm with 100 beats/min, QRS axis at -45^0 and left bundle brunch blook at hospital admission C-sinus rhythm with AV 75 beats/min, left axis deviation, no left bundle branch blook, poor R wave progression in V4-V6 leads and 1 mm ST segment descending depression in DI, DII, aVL, V4-V6 leads.

In October 2014, the patient presented for acute shortness of breath and general fatigue and clinical exam revealed orthopnea, tachypnea, hypoxemia, cold extremities, pallor skin and cyanotic lips and extremities. She had marked jugular venous distention, cardiomegaly, tachycardia, S3 gallop, sistolic murmur of mitral and tricuspid regurgitation, blood pressure of 90/70 mmHg, hepatomegaly with hepatojugular reflux, pulmonary rales, bilateral basal dullness and peripheral edema (legs and sacral). The ECG showed the presence of sinus rhythm, left axis deviation, left bundle branch block. (Fig.1B). Cardiac ultrasound revealed dilated heart cavities, severe tricuspid and mitral regurgitation, global hipokinesis, LV apical thrombus of 7.8 cm^2 surface area, LVEF of 20% and global longitudinal strain (GLS) of -5%. Initial laboratory values showed marked elevated level of NT pro BNP, hepatic and renal dysfunction and moderate trombocytopenia (tabel 1). X-ray examination revealed bilateral pleural effusion in larger quantity on the right hemithorax and a pleural drainage was performed. The pleural effusion was transudate and tumor cells were absent; the tuberculosis etiology was also excluded.

Antineoplastic treatment history, clinical deterioration of cardiac function within 2 months after the last chemotherapy cure and paraclinical investigations led to sustain the diagnosis of heart failure(HF) probably in the context of cancer therapy and treated according to guidelines[1] with 3,125 mg to 6,25 mg o.d of carvedilol o.d., 40 mg of intravenously furosemide on injectomat syringe- 0,04 ml/min for 48 hours, then 20 mg o.d orally, with serum ionogram monitoring, 25 mg o.d to 50 mg o.d of spironolactone, 2,5 mg of ramipril o.d, 0,25 mg of digoxin alternatively with 0,125 mg o.d. She was also given 18 U/kg of heparin with PTT control every 6 hours for 3 days, then 5000 IU of dalteparin every 12 hours for 7 days, 2 mg of acenocumarol o.d with INR monitoring, 20 mg of pantoprazole o.d and 35 mg of trimetazidine b.i.d.

Patient evolution has been favorable, with progressive clinical improvement -increasing effort tolerance and leg edema remission. 6 months after specific HF treatment, echocardiographic examination showed LVEF of 43% and no LV apical thrombus, thus GLS remained reduced (-7,8%). Blood test showed platelet normalization, liver and kidney normal function, high total cholesterol and LDL-cholesterol values. The value of natriuretic peptide and inflammation markers were high, probably in the context of HF and/or neoplasia. ECG revealed the presence of sinus rhythm with

 DOI: 10.12865/CHSJ.41.04.17

AV 75 beats per minute, left axis deviation and no left bundle branch block.(Fig.1C).

A thoracic CT reexamination was performed in February 2015 that described secluded bilateral pleural effusion and no lung metastases.

Discussions

Clinical and laboratory data, chemotherapy treatment history, associated risk factors and favorable condition improvement on HF specific treatment may be arguments for the diagnosis of cardiomyopathy associated with cytotoxic therapy and could be a starting point for discussions on current data regarding differential diagnosis (Table 1).

Tabel 1. Biological parameters evolution

Laboratory tests	October 2014	April 2015		October 2014	April 2015
Complete blood count			**Biochemistry**		
Red Blood Cells /mm^3	4.600.000	3.600.000	Blood sugar (mg/dl)	76	86
Hemoglobin (g/dl)	14.8	12.10	Creatinin (mg/dl)	1.36	0.77
Hematocrit (%)	42	36	Urea (mg/dl)	79	40
MCHC (g/dl)	33	33.6	GFR (ml/min/1,73m^2)	42	84
MCV (fl)	95	99.90	CK-MB U/l	30	
MCH (pg)	33	33.6	Troponin ng/ml	0.01	
White blood cells /mm^3	7.900	6.100	NT-proBNP pg/dl	9000	2000
No. Neutrophiles	4.6	4.10	Cholesterol (mg/dl)	120	229
No. lymphocytes	1.70	1.30	LDL-C (mg/dl)	78	150
No. Eozinophiles	0.20	0.20	HDL-C (mg/dl)	35	54
No. Monocytes	0.60	0.50	Tryglycerides(mg/dl)	69	122
No. Bazophiles	0.02	0.01	ALAT (IU/L)	44	24
Platelets (mm3)	150.000	201.000	ASAT (IU/L)	56	20
ESH mm at 1h/2h	3/6		Ag HBs	negative	
D-dimers mg/L	0,3		Ac Anti VHC	negative	
INR	1.4	2.05	Na+ (mEq/L)	135	137
aPTT “	60	35	K+ (mEq/L)	3.6	5
CRP (mg/dl)	98	38			

The most frequent cardiotoxicity side effects of chemotherapy drugs used for our patient are: myocardial ischemia and infarction for fluorouracil; cardiomyopathy, myopericarditis, arrhythmias for anthracyclines; HF, myopericarditis, arrhythmias for cyclophosphamide; HF, ischemia, arrhythmias for taxanes; thrombosis for tamoxifen and restrictive heart disease, accelerated atherosclerosis and pericardial effusion for radiotherapy[2].

Numerous studies have proved the cardiotoxic effect of anthracyclines (doxorubicin and epirubicin)[3] that can cause type I cardiotoxicity- a form of cardiomyopathy, potentially irreversible and associated with recurrences. Apoptosis and cell necrosis due to cumulative dose effect and direct action on myocardial cell, leads to progressive cardiovascular disease[4].

LV dysfunction appearance may vary from one chemotherapy agent to another. For anthracyclines, this may occur immediately after exposure or later on[5]. However, the heart has significant cardiac reserve, and the expression of cardiac damage may be symptomatic when a substantial amount of myocardial reserve has been exhausted. Therefore, heart damage may become obvious after years or even decades from anthracyclines cancer treatment[6].

Although epirubicin is less cardiotoxic than doxorubicin, Ryberg et al have reported that developing congestive HF risk in a 40 year old woman treated with 800 mg/m^2 of epirubicin was estimated to be 5% [7]. There is considerable variation in chemotherapy treatments cardiotoxic effects susceptibility, HF may occur at lower doses due to phenotypic sensitivity in some individuals[8].

Chronic cardiotoxicity may be taken into account in our case, with no clinical symptoms, with undetectable cardiac dysfunction in a routine cardiac assessment, but subacute cardiotoxicity may also be considered given that symptoms have evolved slowly over a 2 month period following the last cytostatic cure.

The cumulative doses of 728 mg/m^2 epirubicin and 140 mg/m^2 doxorubicin in our patient, the associated risk factors such as mediastinal irradiation, female gender, cytotoxic agents combination with fluorouracil and cyclophosphamide, must have led to cardiac subclinical damage aggravation due to the initial chemotherapy course the patient had been subjected to. Cyclophosphamide, fluorouracil, docetaxel are usually responsible for acute clinical presentation, epirubicin and doxorubicin may be liable for acute, subacute and late cardiotoxicity.

Atherosclerotic coronary ischemia could not be excluded by coronarography. Normal levels of myocardial necrosis enzymes, electrocardiographic appearance with nonspecific repolarization changes, no segmental wall motion abnormalities are not specific for acute myocardial infarction diagnosis, nonaterosclerotic cardiomyopathy diagnosis may be advocated. On the other hand, age of the patient, dyslipidemia (high level of total and LDL cholesterol 6 months after discharged), radiation therapy (often associated with accelerated atherosclerotic coronary artery disease), ovarian suppression treatment (with increased thrombotic risk), cyclophosphamide, fluorouracil and taxanes administration (favoring intracoronary thrombosis and vasospasm) may be causes for possible presence of atherosclerotic coronary artery disease and acute myocardial ischemia.

LV thrombus presence may be a consequence of lower LVEF and may be favored by the use of tamoxifen.

Hepatic and renal dysfunction (Tabel 1) in a patient with previously normal biological parameters, sustains the diagnosis of HF with severely reduced cardiac function confirmed by echocardiographic exploration. Viral etiology of hepatic dysfunction was excluded.

Myocarditis is not usually associated with anthracyclines cardiotoxicity. And yet, typical toxic myocarditis evolution was observed in some patients even though inflammatory infiltration role in cardiotoxicity is controversial [9-11].

The absence of clinical symptoms specific for myocarditis, normal white blood cells number, no eosinophilia, normal cardiac necrosis enzymes (tabel 1), no pericardial fluid, echocardiographic marked dilatation of cardiac chambers and severe LV dysfunction are making myocarditis diagnosis unlikely and advocates for chemotherapy-induced cardiomyopathy for the present case. Endomyocardial biopsy is the gold standard for myocarditis diagnosis. Due to the invasiveness of this procedure, myocardial biopsy was not performed in this particular case. Specific virus detection and cardiac magnetic resonance (CMR) investigation were not available at the time.

According to the American Society of Echocardiography and the European Association -Cardiovascular Imaging expert consensus[12], cancer therapeutics-related cardiac dysfunction is defined as an over 10 % decrease of LVEF assessed through 2D echocardiography (Simpsons method) to a value lower than 53%, with or without symptoms of HF[12].

3D echocardiography evaluation of LVEF demonstrated good temporal variability and is the recommended method for cardiac chemotherapy effect assessment[13]. Longitudinal fibers deformation evaluated through speckle tracking echocardiography - GLS should be used as a predictor of cardiotoxicity, because it is superior to LVEF in detecting chemotherapy induced subclinical cardiac dysfunction[14][15], heart failure patients risk stratification[16][17] and it is easily reproducible. Subclinical cardiac dysfunction could be predicted by changes in molecular or genetic markers and cellular oxidative stress. Biomarkers (such as NT pro BNP)[18], troponin I and T[19][20] are now used for the predictive role of cardiotoxicity development, suggesting subclinical cardiac dysfunction.

In cases where conventional echocardiography cannot assure an accurate cardiac function assessment and a clear decision to discontinue chemotherapy is necessary, CMR[21][22], contrast echocardiography[23] can be used. An integrated approach can lead to increased rate of subclinical cardiac dysfunction diagnosis and prediction of cardiotoxicity[12].

Initial evaluation is recommended and it should include family and personal history, physical examination, ECG, echocardiography (LVEF, GLS) and troponin every time an anthracyclines chemotherapy regime is initiated. When LVEF is under 53%, GLS is below the lower limit of normal on speckle tracking

 DOI: 10.12865/CHSJ.41.04.17

evaluation and/or Troponin I or T is positive, cardiologic evaluation is mandatory. The risk/benefit ratio must be discussed between cardiologist and oncologist, chemotherapy interruption or continuation being the oncologist's decision. Baseline, at the end of therapy and 6 months later, cardiology evaluation is necessary. Once 240 mg/m^2 of anthracyclines is exceeded, LVEF, GLS and troponin should be performed before each 50 mg/m2 additional chemotherapy[12].

In our case it would have been useful to assess GLS and troponin baseline and after the first course of chemotherapy in order to detect a preexisting cardiac dysfunction and influence the second regime in order to limit cardiotoxicity. Although LVEF has improved, GLS value, a more sensitive parameter of cardiac function assessment remained low (a rising from -5% to -7,8% in 6 months- figure 2) which means we should take into consideration a persistent and severe heart damage. Cardiologic evaluation is necessary for our patient every 6 months.

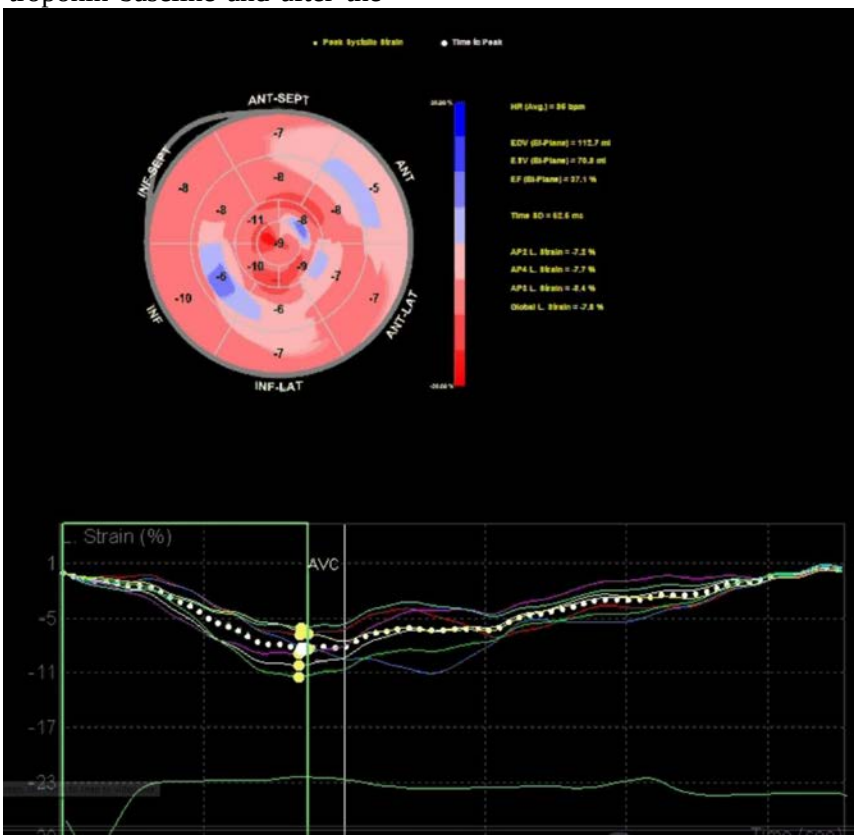

Fig.2. "Bulls eye" after six months of treatment shows marked decrease of longitudinal global strain (-7,8%), diffuse kinetic alteration of all LV segments.

"Bulls eye" (Fig. 2) pattern after six months of treatment shows marked decrease of longitudinal global strain, less specific to a coronary artery territory hypoperfusion, which would rather suggest diffuse kinetic alteration of all LV segments, once more pleading for the diagnosis of chemotherapy induced cardiomyopathy.

In conclusion, chemotherapy cardiotoxicity can be prevented through patient monitoring before, during and after treatment by robust methods for diagnosis and prediction of cardiac dysfunction. A strong collaboration between cardiologist and oncologist is essential for cancer patients monitoring, chemotherapy and radiotherapy schemes optimization, HF treatment and cardiovascular protection.

Acknowledgement

This paper was published under the frame of European Social Found, Human Resources Development Operational Programme 2007-2013, project no. POSDRU/159/1.5/S/136893.

List of abbreviations

CT-Computed Tomography
GLS-Global Longitudinal Strain
LVEF-Left Ventricular Ejection Fraction
LV-Left Ventricle
o.d/b.i.d-Once daily/Twice daily

NT pro BNP-N terminal prohormone of brain natriuretic peptide
ECG-electrocardiogram
HF-Heart Failure
LDL cholesterol-Low density Lipoprotein
2D/3D-Two / three dimension

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Corresponding Author: Cherata Diana-Alexandra, "Filantropia" Municipal Hospital, Strada Filantropiei 1, Craiova, Dolj county, Romania.
Phone: 0040 733 674 763, e-mail: diana_cherata@yahoo.ro

 DOI: 10.12865/CHSJ.41.04.17