Drug-induced toxic Myocarditis: Doxorubicin once again leading to Heart Failure

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Abstract

Treatment protocols in Oncology experienced massive changes in recent decades which have contributed to improve the morbidity and mortality of cancer. However, these advances were often achieved at the expense of significant side effects. The authors describe a case of a 62 year old woman with Follicular non-Hodgkin's Lymphoma who develops a toxic Myocarditis due to Doxorubicin. Anthracyclines cardiotoxicity is an established irreversible complication. There are a few measures that shall be taken into account in order to supervise, prevent and treat these patients.

Keywords: Doxorubicin; Cardiotoxicity; Myocarditis; Heart Failure; Cancer

Palabras clave: Doxorubicina; Cardiotoxicidad; Miocarditis; Insuficiencia Cardíaca; Cáncer

Introduction

The cardiotoxicity of chemotherapeutic agents is a problem that has attracted the attention of clinicians in order to improve monitoring of clinical condition, prevention and treatment of complications. Anthracyclines (eg. doxorubicin) are the most widely pharmacological class related to cardiotoxicity. They are used in lymphomas, leukemias, sarcomas and breast cancer[1]. Their cardiotoxicity is irreversible, cumulative, dose-dependent and it's due to direct lesion/loss of myocites. Heart Failure (HF) can present acutely with high doses but it is most frequently a late-onset complication[2].

Case Presentation

A 62 year old caucasian woman has a medical history of Arterial Hypertension, type 2 Diabetes Mellitus treated with oral hypoglicemic agents and Pulmonary Emphysema. She is diagnosed with grade 3 Follicular non-Hodgkin's Lymphoma and starts a chemotherapy regimen with R-CHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) with a 3-week periodicity. Prior to treatment initiation there was assured adequate control of cardiovascular risk factors, normal sinus rhythm in Electrocardiogram (ECG), negative cardiac biomarkers (troponin I and b-natriuretic peptide [BNP]) and a two-dimensional transthoracic echocardiogram (TTE) without significant abnormalities (left ventricular ejection fraction [LVEF] of 68%, determined by Simpson method).

Two days after the seventh cycle of chemotherapy, the patient was admitted in the Emergency Department (ED) with severe shortness of breath, orthopnea, retrosternal chest pain exacerbated by inspiration and symmetric leg swelling. There were no other symptoms, such as paroxysmal nocturnal dyspnoea or fever.

The physical examination showed tachypneia with use of accessory respiratory muscles, tachycardia, jugular venous distention at 90º (4 cm), decreased breath sounds in the lower third of both lungs and exuberant peripheral edemas. The remainder of the physical examination was otherwise normal.

ECG showed sinus tachycardia, normal PR interval with no depression and no ST segment abnormalities. Arterial blood gases documented a hypoxemic respiratory failure. Laboratory tests *(Table 1)* revealed marked increase of BNP (2291.7 pg/mL) and Troponin I (0.554 ng/mL). Furthermore, there was documented a serum creatinine escalation, representing a type I Cardiorrenal Syndrome. The chest x-ray *(Figure 1)* revealed cardiomegaly, Kerley B lines and right pleural effusion.

Table 1. Laboratory tests results.

Laboratory parameters	ED	3-Month Follow-up	Normal range	Units
Haemoglobin	9.8	13.1	12.0 – 16.0	g/dL
Leucocytes	12.24	5.96	4.0 – 11.0	x 10^9/L
Neutrophils	94.4	46	53.8 – 69.8	%
Platelets	192	100	150 – 400	x 10^9/L
Glucose	102	189	75 – 115	mg/dL
Urea	61	117	10 – 50	mg/dL
Creatinine	1.3	1.17	0.6 – 1.0	mg/dL
Sodium	132	139	135 – 147	mEq/L
Potassium	5.5	5.1	3.5 – 5.1	mEq/L
C-Reactive Protein	4.1	-	< 3.0	mg/L
BNP	2291.7	1025	< 100	pg/mL
Troponin I	0.554	0.174	< 0.08	ng/mL
CK-MB	8	2.8	< 6.4	ng/mL
Myoglobin	349	96.6	< 146.9	ng/mL

The TTE showed severe left ventricular systolic dysfunction with an ejection fraction of 25% (Simpson method), grade III diastolic dysfunction and anterior wall hypokinesis.

A diagnosis of Acute Heart Failure secondary to Anthracycline cardiotoxicity was established.

The patient immediately started therapy with furosemide, beta blocker (nebivolol 5 mg id) and angiotensin converting enzyme (ACE) inhibitor (lisinopril 5 mg id). It was difficult to taper the dose of the prognosis modifying therapy due to arterial hypotension. The patient

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remained without chest pain or *de novo* ECG abnormalities. With excellent urinary output leading to the correction of hypervolemia and respiratory failure, serum creatinine and urea faced a small decline, as well as hyponatremia and hyperkalemia became corrected. We believe the increase in Troponin I must be correlated with the physiopathological mechanism of cardiomyocyte injury by anthracyclines – direct lesion of the cell with loss of myocites – generating a toxic Myocarditis. It was decided not to perform a cardiac catheterization due to the absence of angina or clinical suspicion of coronary disease, and due to the potential nefrotoxicity of contrast agents.

Despite a satisfactory clinical response in the acute setting, the patient remained with exertion dyspnea and was discharged two weeks later with a Class III New York Heart Association functional status. Chemotherapy was suspended and patient remained with haematological surveillance. Three months after discharge, revaluation with a TTE showed deterioration of LVEF to 15%. Serum Troponin I levels were slightly above the upper limit of normal but sill decreasing and it was established a value of 1025 pg/mL as the "dry-BNP" *(Figure 2)*.

Discussion

Anthracyclines may lead to an irreversible (type I) cardiotoxicity. Other drugs (eg. trastuzumab) may encompass a reversible (type II) cardiotoxicity [1,3,5].

This case report represents an early-onset chronic progressive HF secundary to a Toxic Myocarditis, which can occur in around 2% of patients during therapy or within the first year of treatment. Cardiotoxicity is related to a cumulative effect *(Table 2)*. The maximum lifetime cumulative dose for doxorubicin is limited to 400-550 mg/m^2 [1].

Figure 1. Upper panel: X-ray showing cardiomegaly, Kerley B lines and right pleural effusion. Lower panel: X-ray at 3-month follow-up.

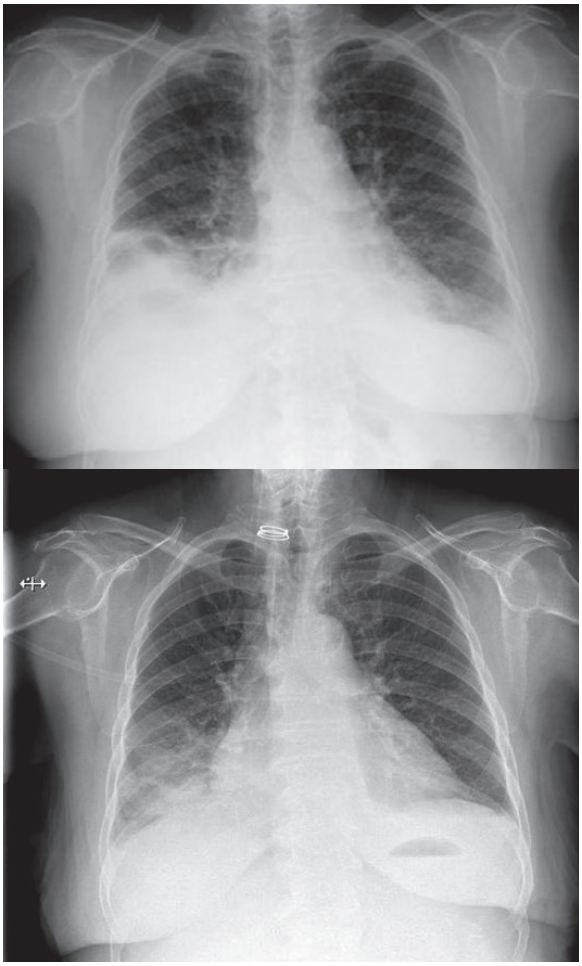

Figure 2. Cardiac biomarkers evolution. Prior to treatment initiation, both Troponin I and BNP were negative. Two days after the seventh cycle of R-CHOP, the patient was admitted in the ED (vertical dashed line) and both BNP and Troponin were rising. The three-month follow up showed a slow progressive decline in Troponin I. *BNP 1025 pg/mL documented as "dry-BNP".

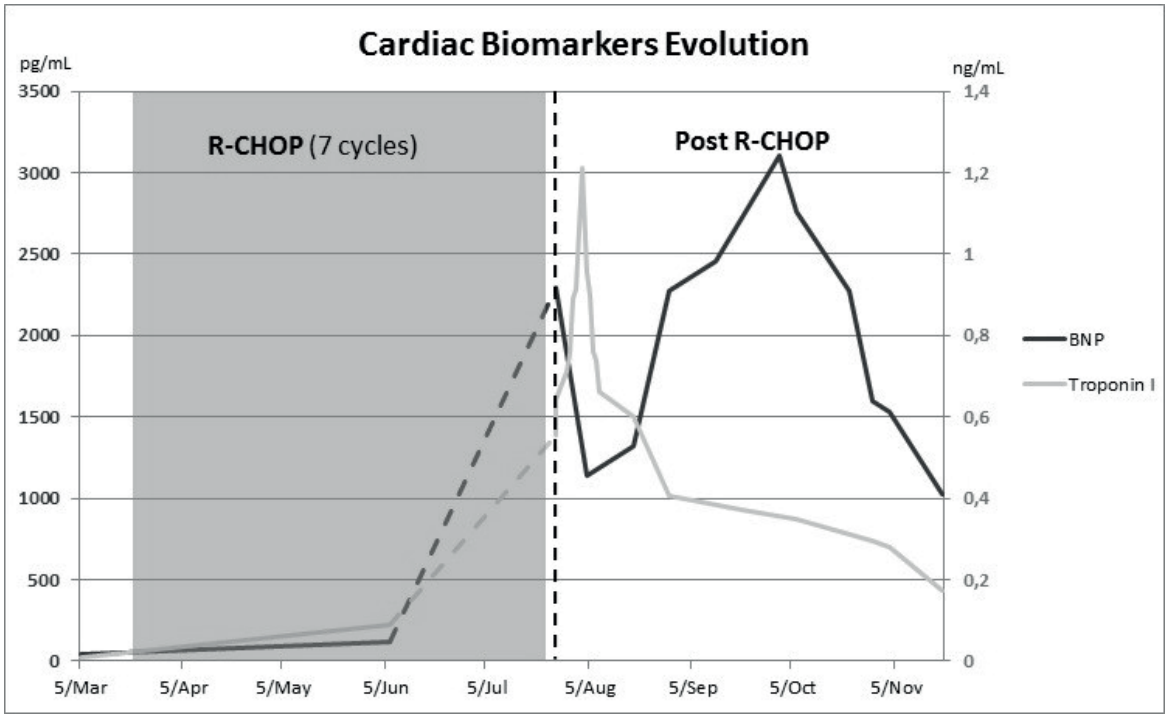

Table 2. Doxorubicin cumulative toxicity[1]

Cumulative dose	Probability of developing HF
400 mg/m2	3-5%
550 mg/m2	7-26%
700 mg/m2	18-48%

Our patient fulfilled 7 cycles of R-CHOP, with a 90 mg doxorubicin dose per cycle, which represents a cumulative dose of 630 mg (below the maximum cumulative dose estimated to the patient – 720 mg). Female gender, concomitant use of cyclophosphamide and age are important risk factors that may have contributed to the harmful effect of anthracyclines in this case. Other conditions may increase cardiotoxicity, such as doxorubicin intravenous bolus administration (instead of perfusion), history of chest irradiation, underlying cardiovascular disease and increase in cardiac biomarkers during and after previous administrations [1,3].

Before treatment initiation, cardiovascular risk assessment is required. Cardiovascular risk factors should be aggressively treated[2] and if cardiotoxicity remains a great concern, an alternative chemotherapeutic regimen with less known cardiotoxicity should be found. Patients must be monitored during and after chemotherapy - late-onset left ventricular dysfunction should always be suspected along their lives[1,5].

Doppler TTE remains the election tool for baseline cardiologic screening and follow up of cancer patients during or after the completion of cardiotoxic regimens.[6]

Some measures may decrease the risk of anthracyclines cardiotoxicity: using the lowest necessary dose as a continuous infusion to reduce peak plasma levels of the drug, avoiding concomitant use of other cardiotoxic drugs and whenever there is evidence of equal efficacy or superiority of non-anthracycline regimens, they should be considered[1].

Lipossomal anthracyclines are associated with a lower incidence of left ventricular dysfunction[3].

A wide variety of drugs are being studied for cardiotoxicity[3]. Dexrazoxan is an intracellular iron chelating agent that acts preventing the anthracycline oxidative stress inductive process. Up to date, this is the only drug approved by FDA for cardiotoxicity prevention[5]. Quercetin is another oxidative stress reducing agent that acts by modulating Bmi-1 expression, therefore decreasing *in vitro* doxorubicin-induced cardiotoxicity. Studies in humans are lacking[7]. Metformin, an oral antidiabetic agent, has proven *in vitro* benefit[8, 9]. Studies in humans are lacking.

Beta-Blockers and ACE inhibitors are drugs extensively studied in HF and they should be used to treat these patients once HF develops. Doses should be increased to maximally tolerated ones. Diuretics (eg. furosemide) should be used to control symptoms of congestion[2].

Assuming the irreversibility of the cardiotoxicity, patient's prognosis is poor.

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