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CASE REPORT

Chemotherapy induced Takotsubo cardiomyopathy

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Abstract

Chemotherapy has been linked with Takotsubo cardiomyopathy. Most of the literature on chemotherapy associated Takotsubo cardiomyopathy is on the drug 5-fluorouracil. In this report, we describe the case of a 55-year-old Asian male who developed Takotsubo cardiomyopathy while receiving dual chemotherapy with cytarabine and daunorubicin for acute myeloid leukemia. To our knowledge, it is the first case of Takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

Key words: Takotsubo cardiomyopathy; Chemotherapy; Cytarabine; Daunorubicin

Core tip: In this case report, we describe first case of Takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

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INTRODUCTION

Chemotherapeutic drugs have a wide range of cardiotoxic effects. Recently, there have been case reports of chemotherapy [namely 5-fluorouracil (5-FU)] induced Takotsubo cardiomyopathy (TC)[1-5]. However, to the best of our knowledge, there has been no published literature on cytarabine and/or daunorubicin causing TC. In this report, we describe the case of a 55-year-old Chinese male who developed TC while receiving dual chemotherapy with cytarabine and daunorubicin for non M3 acute myeloid leukemia.

CASE REPORT

A 55-year-old male with past medical history of diabetes mellitus (type Ⅱ) presented to our hospital with complaints of pleuritic chest pain with non-productive cough and fever (Tmax 101.2 °F) for 3 d. Chest X-ray showed right-sided lung infiltrates. Patient was admitted to the medical floor with the diagnosis of community-acquired pneumonia and was started on moxifloxacin. The patient's blood work showed an incidental finding of 12% blast cells with a total white cell count of 9.9. Electrocardiogram performed on the day of admission revealed sinus tachycardia with abnormal R wave progression. Echocardiogram showed ejection fraction (EF) of 60%-65%, with normal chamber size and mild diastolic dysfunction. Three sets of cardiac enzymes including cardiac Troponin I and creatine kinase-MB were negative. Patient was evaluated by the hematology and oncology team for the incidental finding of blast cells on peripheral blood smear. The next day, as per the hematologist's recommendation, the patient underwent a bone marrow biopsy which showed the presence of pro-myelocytes, suggestive of M3 acute myeloid leukemia. The patient was started on All Trans-Retinoic Acid induction chemotherapy regimen. Prophylactic valacyclovir, omeprazole and intrave-

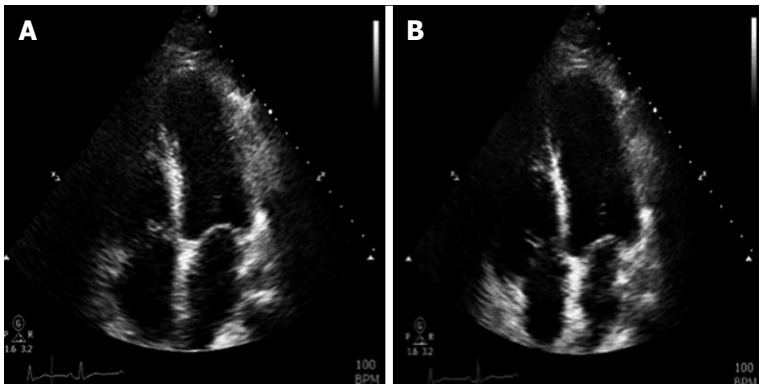

Figure 1 Echocardiogram showing ballooning of the apex with hyper contracted basal segment at end systole (A) end diastolic phase (B).

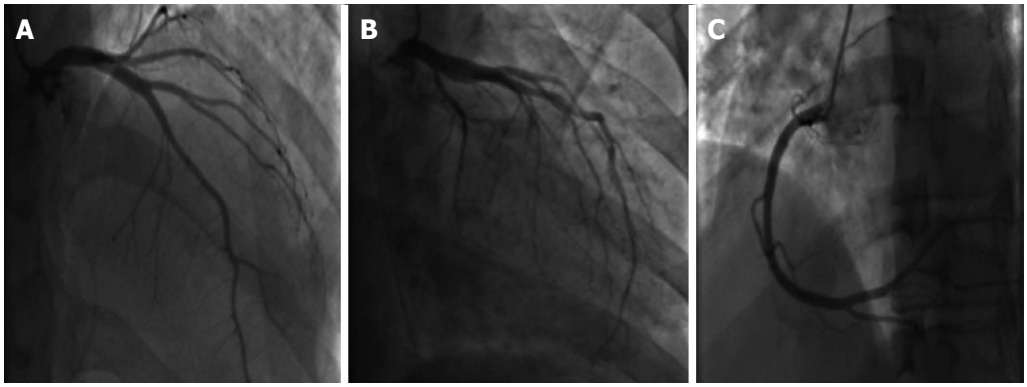

Figure 2 Coronary angiogram showing clean coronaries with thrombolysis in myocardial infarction 3 blood flow left main and left anterior descending (A), left circumflex (B) and right coronary artery(C).

nous (*iv*) fluids were also started.

Two days after the initiation of chemotherapy, fluorescent *in situ* hybridization results demonstrated a negative translocation of chromosomes 15, 17, thus confirming the diagnosis of non-M3. As a result, the chemotherapy regimen was changed to cytarabine 100 mg/m^2 and daunorubicin 60 mg/m^2. On day 6 of chemotherapy with cytarabine and daunorubicin, the patient began to experience non-radiating sub sternal chest pain associated with palpitations. Electrocardiogram obtained at that time showed sinus tachycardia of 170 bpm with ST segment elevation in leads I, aVL, V5, V6; consistent with anterolateral wall ST elevation myocardial infarction (STEMI). The patient was transferred to the cardiac intensive care unit (CCU) with a diagnosis of STEMI. Cardiac enzymes were obtained which showed Cardiac Troponin I of 8.54 upon initial transfer to the CCU, reaching a maximum of 38.64 after 18 h (normal values 0-0.1 ng/mL). Given the patient's immunocompromised state, cardiac catheterization was deferred and he was managed medically with aspirin, clopidogrel, rosuvastatin, and aggressive *iv* hydration. Echocardiogram done on day 6 of chemotherapy showed an EF of 30%-35% with segmental wall motion abnormalities: mild anterior, septal, apical, inferior and lateral wall hypokinesia, with normal diastolic function consistent with mid-left anterior descending artery occlusion (Figure 1). On day 20 of admission, patient underwent an elective cardiac angiogram, which showed non-obstructive coronary vasculature, mildly decreased left ventricular systolic function, EF of 50% with mild anterolateral and anterobasal hypokinesia (Figure 2).

DISCUSSION

This case report demonstrates a strong causal relationship between chemotherapy and the development of TC as evidenced in the patient's presentation on day 6 of chemotherapy induction. Symptomatic recovery of the patient after supportive medical management, with the concomitant discontinuation of the chemotherapeutic agent, also strengthens this causal relationship. The patient's repeat echocardiogram (performed 2 wk after discontinuation of the chemotherapeutic agents) showed a complete recovery of the EF with no wall motion abnormalities. In addition, a coronary angiogram demonstrated non-obstructed coronary vasculature. Given the patient's clinical presentation and the diagnostic evidence obtained, there is no alternative justification for the clinical course observed other than Takotsubo cardiomyopathy. This is the first case report of daunorubicin and/or cytarabine induced TC.

Most of the literature on chemotherapy associated TC is published on the drug 5-FU, a widely used chemotherapeutic agent for solid tumors. One case report from

Japan described daunorubicin-induced TC in a patient with refractory multiple myeloma[6]. However, to our knowledge, this is the first case report of daunorubicin and/or cytarabine induced TC in the United States.

Chemotherapy induces increased sympathetic tone with resulting elevation of cytokine, free radical, prostaglandin, catecholamine and growth factor levels. The excess of these modulators can potentiate worsening adrenoreceptor sensitivity, and can contribute to the clinical presentation of TC[1-5]. Daunorubicin belongs to the anthracycline class of chemotherapeutic agents, which remains among the most active anti-cancer drugs for solid tumor and hematologic malignancies. The exact pathogenic mechanisms responsible for the underlying cardiotoxic effects of anthracycline agents has yet to be elucidated. The current postulated mechanism supports the role of free radical induced cardiac damage (known to be caused by the excessive production of hydrogen peroxide, hydroxyl radicals and reactive oxygen species)[6-10]. These free radicals promote lipid peroxidation which contributes to cell membrane damage, and thus results in the activation of pro-apoptotic enzymes, such as Bax, Cytochrome-c and caspase-3, in myocyte mitochondria, triggering apoptosis and resulting in cardiac myocyte cell death[6-10]. Cardiac myocytes are more susceptible to lipid peroxidation due the presence of a high mitochondrial density with resultant high-energy requirements and the lack of anti-oxidant enzymes, which are required for the detoxification of superoxide anions and hydrogen peroxide. As a result of this cardiac myocyte susceptibility, a dose-related and irreversible loss of cardiac myocytes occurs, resulting in cardiomyopathy[11]. Though the exact mechanism of cardiotoxicity caused by cytarabine has yet to be elucidated, it is postulated that this drug can result in a hypersensitivity reaction or possible immune-mediated damage of cardiac myocyte[12].

In conclusion, we suggest that physicians be vigilant when treating patients with daunorubicin and/or cytarabine and should be aware of a possible association of these chemotherapeutic agents with TC.

COMMENTS

Case characteristics

A 55-year-old male receiving treatment with Daunorubicin and Cytarabine for non M3 acute myeloid leukemia (AML) experience non-radiating sub sternal chest pain associated with palpitations on 6th day after chemotherapy.

Clinical diagnosis

Acute coronary syndrome.

Differential diagnosis

ST segment elevation myocardial infarction (STEMI), non-STEMI, Unstable Angina, Aortic Dissection, Pulmonary embolism, cardiomyopathy, Ventricular wall rupture.

Laboratory diagnosis

Cardiac troponin I and creatine kinase-MB elevation with continued uptrend, consistent with myocardial ischemia.

Imaging diagnosis

Electrocardiogram-anterolateral STEMI; Echocardiogram (ECHO) at day 6 of therapy-ejection fraction (EF) of 30%-35% with segmental wall motion abnormalities; repeat ECHO (two weeks later)-Normalization of EF and no wall motion abnormalities; cardiac catheterization (two weeks later)-clean coronaries. Pt diagnosed with Takotsubo cardiomyopathy.

Treatment

Due to patient's immunocompromised state, he was medically managed with aspirin, clopidogrel, rosuvastatin, and aggressive intravenous hydration in cardiac intensive care unit.

Related reports

Patient initially thought to have acute coronary syndrome but was eventually found to have Takotsubo cardiomyopathy. Patient had clean coronaries on Cardiac catheterization and on repeat ECHO, his EF normalized and wall motion abnormalities resolved.

Term explanation

Non M3 AML-According to French-American-British classification acute myeloid leukemia are sub grouped in to 8 categories M0-M7. This classification guides the therapy and prognosis in patients diagnosed with AML.

Experiences and lessons

Vigilance should be observed while treating patients with daunorubicin and/or cytarabine.

Peer review

This is first case report of takotsubo cardiomyopathy associated with daunorubicin and/or cytarabine.

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