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Case Report

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Tako-tsubo Cardiomyopathy in Oncology Clinical Trials

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Abstract

Tako-tsubo cardiomyopathy is a rare reversible clinical disorder that is characterized by transient left-ventricular dysfunction. Diagnosis is based on Mayo Clinic diagnostic criteria and is confirmed with coronary angiography. Various risk factors have been described with the leading role of emotional or physical stress. Tako-tsubo cardiomyopathy in cancer Patient is frequently attributed to either the main disease or chemotherapy. We described 3 cases of Tako-tsubo cardiomyopathy observed in clinical trials-in patients with non-small cell lung cancer, diffuse large B-cell lymphoma, and cholangiocarcinoma. We conclude that a diagnosis of an advanced cancer could be an additional independent risk factor and a possible trigger for developing of Tako-tsubo cardiomyopathy. Considering this, in patients with cancer who are referred to emergency room with complaints of chest pain/discomfort and/or dyspnea, and who are suspected of having acute coronary syndrome, differential diagnosis should include Tako-tsubo cardiomyopathy. Assessment of causality relationship should be accurately performed in clinical trials as some data from the literature suggest possible causal relationship to certain chemotherapeutic agents.

Keywords: Tako-tsubo cardiomyopathy, Cancer, Lung cancer, Non-Hodgkin lymphoma, Cholangiocarcinoma.

Introduction

Tako-tsubo cardiomyopathy (TCM) ('broken-heart syndrome', stress cardiomyopathy, stress-induced cardiomyopathy, apical ballooning syndrome) is a rare reversible stress-induced clinical disorder characterized by transient left-ventricular dysfunction and apical akinesis [1]. Clinical presentation is characterized by acute chest pain and electrocardiographic abnormalities which are indistinguishable from acute coronary syndrome. The diagnosis is based on Mayo Clinical criteria and is typically confirmed with coronary angiography [2]. Several mechanisms have been proposed to describe development of Tako-tsubo cardiomyopathy, however the exact etiology is unknown. Emotional or physical stress is thought to be the most common trigger of this disease. During the past several years, we observed increasing evidence of Tako-tsubo cardiomyopathy in cancer patients, which is assessed by some authors as related to either the disease, or chemotherapy [3-5]. This is especially important in clinical trials, where the correct diagnosis and causality assessment influence, not only treatment of a particular patient, who experienced TCM, but also the whole program of drug development. Herein, we present three cases of TCM diagnosed in cancer patients who were enrolled in oncology clinical trials.

Case 1

An 82-year-old man with metastatic non-small cell lung cancer (NSCLC), diagnosed in 2014 and treated with carboplatin and gemcitabine followed by palliative left upper and lower lobectomy. His medical history included: arterial hypertension, myocardial infarction, prostate cancer, and actinic colitis. Concomitant medications included: lansoprazole, Ramipril, bisoprolol, Plavix (clopidogrel), Torvasr (atorvastatin), dexamethasone, ranitidine, and granisetrone. In 2015, he was enrolled in a clinical trial and 14 days after initiating chemotherapy with pemetrexed presented to the emergency room with dyspnea, retro-sternal discomfort, and asthenia. The ECG at admission demonstrated atrial fibrillation with ventricular rate of 95 bpm, ST-segment elevation in V2-V6 and biphasic T waves in V2-V5 (it is important to Mention that his screening ECG was unremarkable with sinus rhythm and ventricular rate of 62 bpm). Troponin T was elevated up to 0.6 ng/mL (reference ranges 0-0.48) and proBNP up to 5298 pg/ml (reference range <100 pg/mL). Echocardiography revealed decreased left ventricular ejection fraction (LVEF) of 45% with apical akinesis. Cardiac catheterization showed normal coronary arteries, no evidence of coronary arterial stenosis and confirmed apical akinesis with left ventricular ejection fraction (LVEF) of 40%. These findings were consistent with Tako-tsubo cardiomyopathy. The patient received supportive care with rapid clinical improvement. Follow up ECG showed sinus rhythm with heart rate of 60 bpm and deeply inverted T waves in V2-V6. Subsequent echocardiography found absence of dilation of the left ventricle, apical

akinesis and front median akinesis with LVEF of 40%. The event was considered resolved and the patient was discharged home after a 7-day admission in good clinical condition. He had no clinical signs of congestive heart failure during follow-up observation. After resolution of the event, the patient was continued on pemetrexed in the study.

Case 2

A 77-year-old female with stage III diffuse large B-cell lymphoma (DLBCL) diagnosed in 2009. Medical history was remarkable for grade 1 arterial hypertension, anxiety, and stroke in 2009. Concomitant medications included: bisoprolol, lansoprazole, amlodipine, and phenobarbital. She performed cardiac ultrasound in accordance with the study protocol 5 days after chemotherapy with the investigational drug. The patient was asymptomatic and in good general condition. ECHO showed left ventricular apical akinesis with LVEF of 45%. The patient was admitted to the hospital for further evaluation. Laboratory tests showed Troponin T of 0.02 ng/ml (reference ranges 0.000-0.080), CPK of 54 U/l (reference range 0-14), CKMB of 0.48 mg/ml (reference range 0.00-5.00), and myoglobin of 31 ng/ml (reference range 3-110). Coronarography performed 6 days later did not reveal obstructive coronary artery disease and showed normal kinesis of the left ventricle. The patient was diagnosed with TCM, not related to chemotherapy. The patient was discharged after an eight-day admission and a follow-up ECHO performed 16 days after the event the initial presentation, showed normalization of LVEF-60%. The patient was continued on chemotherapy. Four months later the patient again showed decrease of LVEF to 30% and troponin T elevation up to 0.285 ng/ml. She was admitted to the hospital with a diagnosis of a heart failure and was discharged after a 1-week admission. She was discontinued from the study 2 months after that (or 6 months after the diagnosis of TCM) due to progression of DLBCL.

Case 3

A 64-year-old female patient with metastatic cholangiocarcinoma, diagnosed in 2013. Medical history was remarkable for arterial hypertension, paroxysmal atrial fibrillation, dyslipidemia, and stroke in 2013. Concomitant medications included: Ramipril, bisoprolol, rosuvastatin, enoxaparin sodium, and dalteparin. A multigated acquisition (MUGA) scan and ECG performed during screening was normal. LVEF was 63%, and troponin T was 10 ng/L (reference ranges 0-14.99). The patient was randomized into a clinical trial. Ten days after initiation of therapy, She experienced a pressure-like feeling in the chest and was admitted to the hospital on the same day. The ECG done at admission revealed ischemic changes and sinus tachycardia with heart rate of 114 bpm. Cardiac ultrasound showed ischemic changes with EF of 43%. Coronary angiography ruled out ischemic nature of the event and also did not show obstructive coronary artery disease. Diagnosis of TCM was made and it was considered to be related to the study treatment by the investigator. Treatment included acetylsalicylic acid and diuretics. Patient's condition improved and she was discharged from the hospital 3 days after admission. Several days later, progression of cancer was diagnosed.

Discussion

The incidence of anticancer-treatment induced cardiotoxicity varies widely and depends on the therapeutic regimen and patient's co-morbidities. Anticancer drugs with known cardiotoxic effects include 5-fluorouracil, trastuzumab, lapatinib, sunitinib, bevacizumab, etc. [3-7]. Cardiac-related adverse events may result from different effects: ischemia, hypertension, and arrhythmia. The main and sometimes the only clinical sign of cardiac adverse events, is chest pain or chest discomfort. The incidence of emergency room admissions due to chest pain in the US is assessed as 6 mln annually [8]. Only 20-25% of these patients are finally diagnosed with myocardial infarction [9]. Differential diagnosis of chest pain is broad and includes cardiovascular (aortic dissection, pericarditis, myocarditis, TCM), musculoskeletal (rib fracture, neuropathic pain, costochondrosis), pulmonary (pneumonia, pulmonary embolism, tension pneumothorax, pleurisy), gastrointestinal (cholecystitis, pancreatitis, esophageal spasm, peptic ulcer disease), and psychiatric (anxiety, depression, somatization and psychogenic pain disorder) conditions [10].

Tako-tsubo cardiomyopathy, also known as stress-induced cardiomyopathy is a relatively rare condition, first described in 1991 by Dote and colleagues [11]. Now, the International Tako-tsubo Registry, a consortium of 26 centers in Europe and the United States, was established at University Hospital Zurich, and the number of publications describing TCM is increasing. Currently, more than 1750 TCM cases have been described [1].

The first case of TCM in cancer patient was reported by Gangadhar T, et al. in a patient with esophageal cancer. Since then, it was described in patients with different colorectal cancer, lung cancer [3-5,12-14]. Some authors were focusing on chemotherapeutic agents administered to the patients, seeking a relationship between treatment and TCM-5-Fluorouracil, bevacizumab [3-5].

Predisposing factors are still under discussion with documented high prevalence (up to 56%) of chronic anxiety disorders that antecedes the onset of cardiomyopathy [15]. Peliccia, et al. showed that emotional stressors preceded TCM in 39% of patients and physical stressors in 35% [16]. Templin et al. reported prevalence of physical triggers that were more frequently present than emotional triggers (36.0% vs 27.7%), whereas, 7.8% of patients had both triggers, and in 28.5% of cases, TCM occurred without any evident trigger [1]. Risk factors include: obesity (17%), hypertension (54%), dyslipidemia (32%), diabetes (17%), and smoking (22%) [16]. It is important to note that the prevalence of neurologic or psychiatric disorders was 46.8%, making it the most important risk factor. The predominant symptoms on admission are chest pain (75.9%), followed by dyspnea (46.9%) and syncope (7.7%) [1].

Diagnosis is usually based on Mayo Clinic diagnostic criteria, all of which are required for the diagnosis [2]:

1. Transient left ventricular (LV) dysfunction (hypokinesis, akinesis, or dyskinesia) involving the apical and/or midventricular myocardial segments with wall motion abnormalities extending beyond a single epicardial coronary distribution.
2. Absence of obstructive coronary disease or angiographic evidence of acute plaque rupture that could be responsible for the observed wall motion abnormality.
3. New electrocardiographic abnormalities (ST-segment elevation and/or T wave inversion) or elevation of cardiac troponin.
4. Absence of pheochromocytoma or myocarditis.

Treatment: no therapies have been shown to be beneficial, but nitrates are used for pulmonary edema, intraaortic ballon pump for low output, combined alpha- and beta- blockers if hemodynamically stable and magnesium for arrthymias related to QT prolongation. It is generally considered that beta-blockers might prevent TCM [17], however, more recent data do not support this, reporting that TCM was seen in 32.5% of patients while they were taking these agents [1].

This hypothesis has been confirmed in our study-all 3 patients were receiving beta-blockers at the time of the diagnosis.

One of our patients was male, which is atypical, as 89.8% of TCM patients are women [1]. Interestingly, in papers that describe TCM in oncology patients, males are represented more broadly [3,4], but women still predominate-76% in accordance with the data from study conducted by Vejpongsa, et al. [18]. It allows to think that presence of oncological disease is a more powerful risk factor, than sex. All 3 cases had risk factors, such as arterial hypertension (all 3 patients), history of stroke or myocardial infarction, and atrial fibrillation. Only one patient had a medical history of anxiety. However, none of the previous authors investigated the incidence of cancer history in patients with TCM. Vejpongsa et al. considered TCM in cancer patients to be usually triggered by surgical procedure and less commonly by chemotherapy [18]. It is known that emotional stress of living with a diagnosis of cancer and its treatment, fear of recurrence, and the distress imposed by living with the day-to-day physical problems, can create new or worsen preexisting psychological distress for people living with cancer [19]. Chronic psychological stress may be a risk factor, whereas acute anxiety may ultimately trigger the syndrome [15]. We should also consider a possibility of pain crises which are often seen in patients with cancer, and can lead to the development of TCM [14]. These 3 patients had different malignancies, but all were advanced or metastatic after 1-2 previous lines of therapy. We speculate that such patients could be considered to be in a chronic stress condition, which can worsen depending on the success of therapy.

It is interesting that one patient (case 2) was asymptomatic at the time when laboratory symptoms of TCM were revealed.

An important point to consider when TCM is diagnosed in a study subject-whether it is related to study therapy or not. There is a significant amount of data, that TCM may be a result of exposure to chemotherapeutic agents, such as 5-fluorouracil, bevacizumab, cetuximab, rituximab, doxorubicin, and cyclophosphamide [3,5,6]. In 1 of 3 our cases, the investigator considered the event of TCM to be related to the study chemotherapy.

Conclusion

A diagnosis of cancer should be an additional independent risk factor and a possible trigger for developing of TCM. Considering this, in patients with cancer who are referred to emergency room with complaints of chest pain/discomfort and/or dyspnea, and who are suspected of having acute coronary syndrome, differential diagnosis should include TCM. Assessment of causality relationship should be accurately performed in clinical trials as some data from the literature suggest possible causal relationship to certain chemotherapeutic agents.

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