Takotsubo Cardiomyopathy Following Initial Chemotherapy Presenting with Syncope and Cardiogenic Shock – a Case Report and Literature Review

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Abstract

Anthracyclic chemotherapeutic agents have been demonstrated to cause myocyte apoptosis leading to a dose-dependent reduction in left ventricular (LV) function. There are also case reports of rapidly developing heart failure after an initial course of chemotherapy but it is uncertain as to whether the mechanism for LV dysfunction is similar. We present a case of Takotsubo cardiomyopathy (TC) developing five days after receiving the first cycle of chemotherapy consisting of rituximab, prednisone, doxorubicin, cyclophosphamide and vincristine (R-CHOP). The patient was an 85 year old woman admitted with cardiogenic shock and syncope with clinical picture suggestive of an acute coronary syndrome. Cardiac catheterization however, demonstrated no significant coronary artery disease but with unique LV apical ballooning consistent with TC. She stabilized with supportive therapy and serial echocardiograms showed normalization of LV function. She was subsequently rechallenged with R-CHOP without any deterioration in LV function. As to the best of our knowledge, this is the first reported case associating R-CHOP with TC. This case supports the concept that TC may be an idiosyncratic response to chemotherapy and our successful rechallenge with R-CHOP provides a unique insight into the feasibility of safe re-administration of chemotherapy to patients recovering from TC.

Background

Takotsubo cardiomyopathy (TC) is an uncommon acute syndrome that mimics ST-segment elevation myocardial infarction. It is characterized by dynamic electrocardiographic changes associated with transient, severe left ventricular wall motion abnormalities not attributable to obstructive epicardial coronary disease in a pattern that involves the mid and apical segments of the heart in all coronary distributions. It is typically felt to be precipitated by emotional or physical stress and more common in elderly women than men. Here we report a case of TC presenting as syncope and cardiogenic shock five days following an initial course of chemo-immunotherapy that included treatment with liposomal doxorubicin and with clinical and imaging features consistent with TC.

Case Report

An 85 year old white woman was admitted following an episode of syncope. She had a history of bullous pemphigoid, dyslipidemia and longstanding history of chronic lymphocytic leukemia, which was recently diagnosed to have progressed to diffuse large cell lymphoma. She denies any prior cardiac history or intervention. One month prior to her current admission, she was seen at an outside facility for syncope occurring after an elective lymph node biopsy. Her workup was essentially normal, including serial cardiac enzyme evaluation, 2-D echocardiogram and persantine nuclear stress imaging. A 12-lead electrocardiogram (EKG) showed no acute changes. The stress imaging showed no evidence of myocardial ischemia and the LV ejection fraction (LVEF) was 60%. Her in-patient course was unremarkable and she immediately returned to her baseline without any recurrence of syncope. She was discharged after 72 hours of hospital stay with a diagnosis of vasovagal syncope. Lymph node biopsy results revealed transformation of chronic lymphocytic leukemia to large cell lymphoma.

She underwent her first cycle of R-CHOP chemotherapy in an outpatient setting which consisted of rituximab (300 mg IV), cyclophosphamide (1000 mg IV), liposomal doxorubicin (50 mg IV), vincristine (1 mg IV) and prednisone (100 mg PO for 5 days). Five days later she had a transient episode of mild substernal chest discomfort that was characterized as pressure-like sensation with radiation to the jaw and shoulder (=12 hours prior to current hospitalization). She did not seek medical care at that time. The following day, she complained of dizziness, diaphoresis and reported loss of consciousness for 5-10 sec for which she was evaluated by emergency medical personnel on-site and transferred to our institution within 30 min. Emergency room evaluation showed no evidence of arrhythmia. She was noted to be hypotensive (88/60 mmHg) and tachycardic (113 bpm). Physical examination revealed jugular venous distension, bibasilar pulmonary crackles, and an S4 gallop with no peripheral edema. Significant laboratory findings included neutropenia (WBC count of 2,800 cells/ml, and absolute neutrophil count of 670 neutrophils/ml). Initial troponin I was marginally elevated at 0.75 ng/ml with normal creatine kinase (36 units/L). The ECG on admission (Figure 1A) showed normal sinus rhythm with QS complexes in leads V1-V3, 1-2 mm ST segment elevations in the same leads and biphasic T waves in leads V4, V5.

The initial differential diagnoses included syncope/cardiogenic shock in the setting of an acute coronary syndrome versus sepsis in an immunocompromised host. Her echocardiogram revealed marked apical hypokinesis with preserved basal segmental motion and an estimated LVEF of 20%. Following hemodynamic stabilization, she underwent left heart cardiac catheterization (Figure 2), which revealed...
absence of any significant obstructive coronary artery disease (CAD). Left ventriculography was consistent with echocardiographic findings demonstrating severe apical ballooning. Cardiac MRI also showed apical ballooning and absence of gadolinium-delayed hyperenhancement consistent with viable myocardium (Figure 3). During her hospital course, she responded well to norepinephrine intravenous infusion for hemodynamic support along with empiric broad-spectrum antibiotics. Multiple blood samples showed no bacterial growths and norepinephrine was slowly tapered off. Subsequent ECGs revealed dynamic changes with the appearance of deeply inverted anterior T waves in leads V3 to V6 (Figure 1B). Troponin I peaked at 4.92 ng/ml, total creatine kinase at 205 units/L and creatine kinase MB at 49 ng/ml. Cardiac MRI confirmed echocardiographic findings of apical ballooning without any evidence of infarction. In the absence of significant CAD and with characteristic apical ballooning, she was diagnosed as a case of takotsubo cardiomyopathy (TC). Due to the strong association of TC with emotional/physical stressors, we furthered queried the patient regarding recent stresses. She specifically denied any history of emotional or physical stressors that could be identified as a precipitating event.

Her clinical course was complicated with the development of bilateral pleural effusions and paroxysmal atrial fibrillation that reverted back to sinus rhythm. Amiodarone was started to prevent recurrence of atrial fibrillation and warfarin for long-term anti-coagulation. She also underwent diagnostic and therapeutic thoracentesis, which revealed a transudative pattern without any evidence of malignancy. She progressively improved over the subsequent week and was started on standard therapy for congestive heart failure. She was discharged home after 10 days, at her baseline function and without clinical evidence of heart failure.

On follow-up, she had quickly returned to her previous activity level with no signs or symptoms of heart failure. Repeat echocardiogram 2 months after discharge, showed an LVEF of 50% with only mild residual hypokinesia of the apical segments. Serial evaluation revealed continued improvement in LVEF (Figure 4) with complete normalization occurring 8 months after initial diagnosis, a time frame consistent with the natural history of TC.

Due to the uncertainty whether this incident represents an idiosyncratic TC or doxorubicin-induced cardiotoxicity, chemotherapy was held but unfortunately her lymphoma also has progressed. With the normalization of LVEF and the typical apical ballooning pattern of TC, direct doxorubicin cardiotoxicity was felt to be unlikely. Due to the paucity of data regarding risk of recurrence with TC and the limited alternatives for treating her large cell lymphoma, a decision was reached to rechallenge with R-CHOP using incrementally increasing doses of liposomal doxorubicin with close monitoring of cardiac function and troponin I levels (Table 1). The slow escalation in doses was empiric since data from the literature is limited. This allowed close monitoring of cardiac function and early recognition of potential cardiac toxicity. Serial echocardiograms did not show any deterioration in LVEF and no elevation of cardiac enzymes noted.

![Figure 1: 12-lead ECG demonstrating dynamic ST-T wave changes. Panel A (day 1 of admission) demonstrated QS complexes with more 1-2 mm ST segment elevations in leads V1-V3 and biphasic T waves in leads V4- V5. Panel B (day 2) showed new deep T wave inversions in the anterior leads (V3 to V6).](image-url)
Literature Review and Discussion

This case report presents several unique features that may shed light on potentially divergent mechanisms contributing to heart failure following chemotherapy. Noninvasive studies documented three weeks prior to the development of heart failure allowed temporal analyses of ECG and echocardiographic changes. In addition, after normalization of ventricular function, a closely monitored protocol to rechallenge with chemotherapy is presented that provides an alternative strategy in patients with prior diagnosis of TC. This case offers meaningful insights regarding risk of TC recurrence and the viability of successfully rechallenging with chemotherapy without any adverse cardiac effects.

TC has been formally defined as a “disease exhibiting an acute left ventricular apical ballooning of unknown cause” [1]. Operationally, the diagnosis is made with pathognomonic findings of transient left ventricular apical hypokinesis on echocardiography with normal coronary arteries. Initially identified in Japan in the 1990s, “Tako tsubo” refers to a “Japanese octopus trap”, to describe the unique LV morphology on echocardiogram showing a round bottom and narrow neck [2]. Although there is still no universal diagnostic criteria, the proposed modified Mayo Clinic criteria for diagnosis of TC has 4 components: (a) transient hypokinesis, dyskinesis, or akinesis of the LV mid-segments with or without apical involvement; the regional wall motion abnormalities extend beyond a single epicardial vascular distribution; a stressful trigger is often, but not always, present; (b) absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (c) new ECG abnormalities (either ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level; (d) absence of pheochromocytoma or myocarditis [3].

Clinical presentation is usually precipitated by intense emotional/physical stress (e.g. argument, accident, unexpected medical news or surgical procedure). It has been alternatively labeled as “Broken Heart Syndrome” or “Stress-induced cardiomyopathy” [4]. While this clinical condition has only recently been recognized in Western society, it is an increasingly common etiology of acute left heart failure. In a large multi-center international report describing 40 patients, Fazio and associates [5] found that almost 85% of patients present with chest pain or dyspnea. Syncopal episodes as in this patient, are less frequently reported (8%). Rarely, hypotension, cardiogenic shock and cardiac arrest can occur. Elderly women, account for 90% of patients with a mean age of 69 years [2,6]. ECG findings often provide misleading information, with ST segment changes mimicking acute myocardial infarction. In the Fazio series, almost 80% have significant ST segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin level; (d) absence of pheochromocytoma or myocarditis [3].

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important differential diagnosis [3]. Other reported ECG changes are T wave inversion, QT prolongation and abnormal Q waves [7,8]. The overall outcome of TC is favorable, provided that patients survive the initial period of severe heart failure, which can be accompanied by fatal sequelae such as cardiogenic shock and ventricular arrhythmias. In-hospital mortality has been reported to be in the range of 1-2% [9]. However, an overwhelming majority results in complete resolution with left ventricular systolic function normalizing within 1-5 weeks.

The pathophysiologic mechanism of TC is not completely understood. Some investigators believe that transient coronary occlusion or spasm especially with a “wrap-around” left anterior descending artery (LAD) can account for the echocardiographic findings [10]. In support of this theory, a series of typical TC patients who underwent intravascular ultrasound revealed evidence of plaque rupture in the mid LAD [11]. However, most investigators believe that neurohumoral activation is the conceptual basis of TC. This is consistent with findings of excessive sympathetic stimulation as evidenced by high levels of circulating catecholamines which can cause direct myocardial injury or precipitate prolonged ischemia [12]. Although other echocardiographic morphology has been reported, there is a propensity for apical involvement with sparing of the basal segments. Dec in an editorial [13] postulated several theories to explain for this “apical hyper-responsiveness”, including: morphologic absence of a three-layered myocardium in the apex, decreased apical coronary circulation and increased β adrenergic receptor density in the apex.

Physical and emotional stressors that precipitate TC usually occur within the 48 hours preceding hospital admission [5]. The recent diagnosis of large cell lymphoma most likely was devastating for our patient, but it preceded her presentation by 3 weeks and probably was not the precipitating factor since she had normal noninvasive cardiac studies at that time. Although the patient denied any stress associated with her chemotherapy, the emotional response to a novel experience performed under close monitoring of cardiac function. This highlights the potential importance in distinguishing apical ballooning from global cardiomyopathy secondary to cardiototoxic chemotherapeutic agent exposure to chemotherapeutic agents would make it unlikely to be the cause of cardiomyopathy.

Conclusion
We report a case of TC presenting with syncpe and cardiogenic shock several days after receiving the initial course of R-CHOP. This case included several key features frequently seen with TC, an elderly woman presenting as possible acute coronary syndrome, ST segment elevation with mild elevations in cardiac enzymes and pathognomonic apical ballooning on echocardiography without significant CAD. Chemotherapeutic agents are known to cause cardiomyopathy. TC may represent a form of cardiac dysfunction within the spectrum of chemotherapy-induced cardiac toxicity that differs from the more common cumulative-dosing toxicity. Our ability to rechallenge this patient with R-CHOP, without detrimental effects to cardiac function, demonstrates that with close monitoring re-exposure to chemotherapy may be safely instituted. However, it should be emphasized, that rechallenging with chemotherapy after an episode of TC should only be considered if no other viable options are available and this should be performed under close monitoring of cardiac function. This highlights the potential importance in distinguishing apical ballooning from global drug-induced LV dysfunction. TC should therefore be considered in patients developing acute heart failure at a time when cumulative exposure to chemotherapeutic agents would make it unlikely to be the cause of cardiomyopathy.

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References


