Journal of Clinical & Experimental Cardiology

Fernandez et al. J Clinic Experiment Cardiol 2011, 2:2
DOI: 10.4172/2155-9880.1000124

Case Report Open Access

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

Stanley F. Fernandez[1], Manreet Basra[1] and John M. Canty Jr[2]*

[1]Department of Veterans Affairs Western New York Health Care System
[2]Department of Medicine at the University at Buffalo, NY, US

Abstract

Anthracycline 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 (ECG) 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 (sinus tachycardia, 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 to 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

***Corresponding author:** John M. Canty Jr., MD, Biomedical Research Building, Room 347, Department of Medicine/Cardiology, University at Buffalo, 3435 Main St, Buffalo, NY 14214, E-mail: canty@buffalo.edu

Received January 12, 2011; **Accepted** February 21, 2011; **Published** February 23, 2011

Citation: Fernandez SF, Basra M, Canty JM Jr (2011) Takotsubo Cardiomyopathy Following Initial Chemotherapy Presenting with Syncope and Cardiogenic Shock – a Case Report and Literature Review. J Clinic Experiment Cardiol 2:124. doi:10.4172/2155-9880.1000124

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 hypokinesis 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.

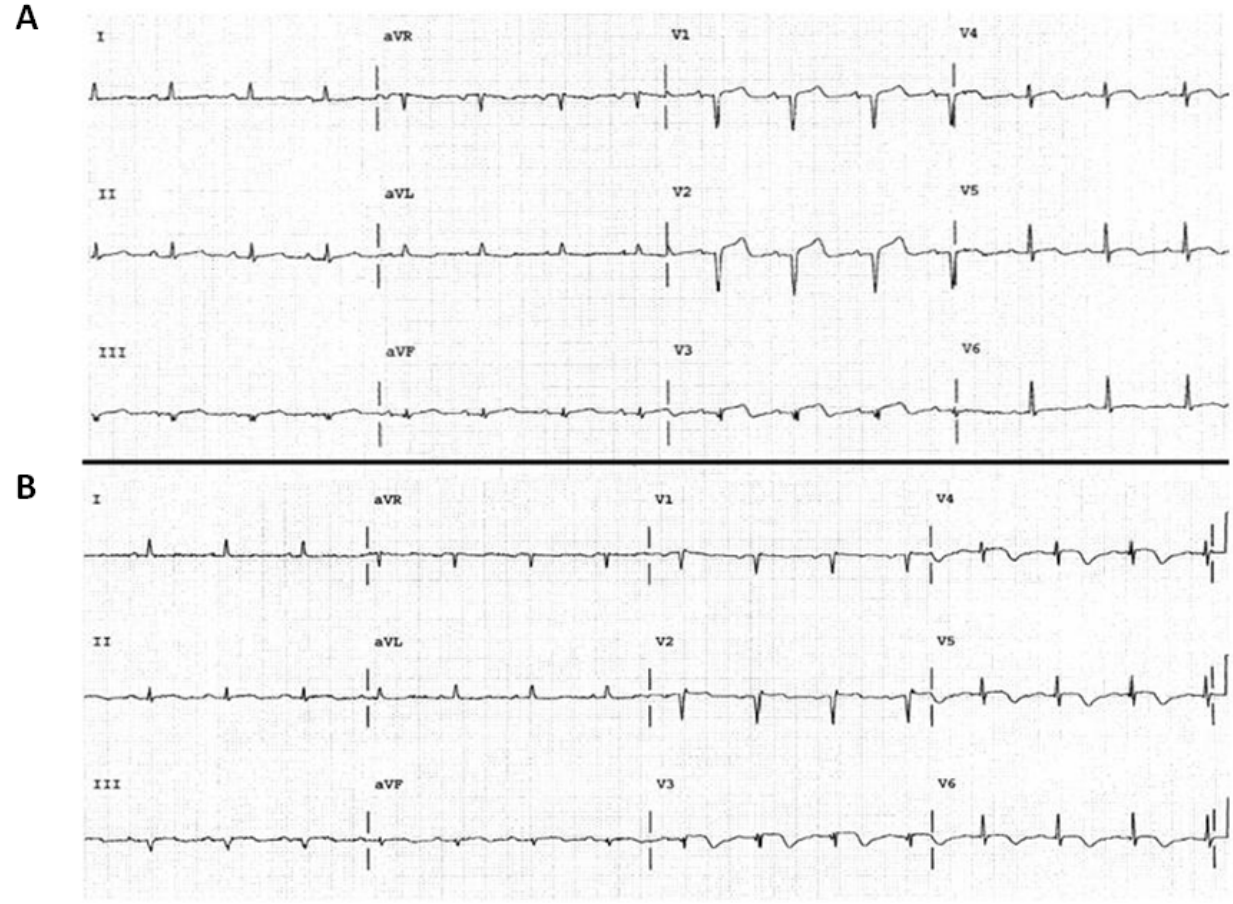

Figure 1: 12-lead ECG demonstrating dynamic ST-T wave changes. Panel A (day 1 of admission) demonstrated QS complexes with more 1-2 mm ST segment elevations in leads V1-V3 and biphasic T waves in leads V4- V5. Panel B (day 2) showed new deep T wave inversions in the anterior leads (V3 to V6).

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,

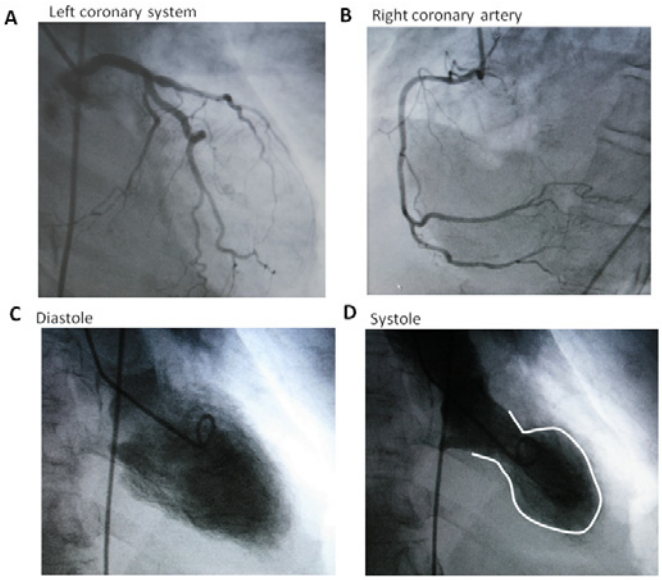

Figure 2: Cardiac catheterization images did not demonstrate any significant disease in the left anterior descending and circumflex system (panel A) and right coronary artery (panel B). Left ventriculogram from the right anterior oblique projection at the end of diastole (panel C) and systole (panel D) demonstrated severe hypokinesis of the inferoapical and anteroapical wall (apical ballooning) with preserved basal segmental wall motion consistent with TC.

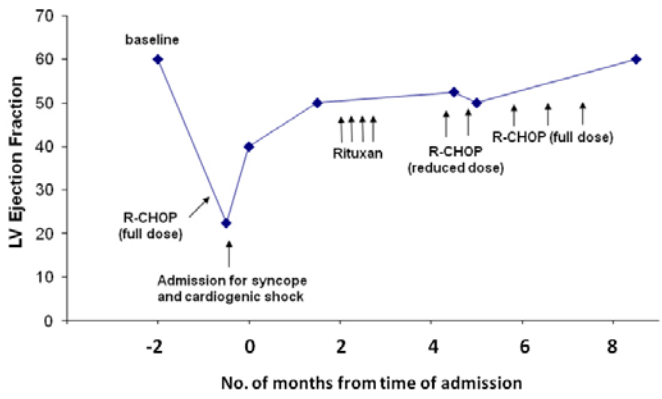

Figure 3: Cardiac MRI showing left ventricular cavity during diastole (panel A) and systole (panel B). Normal LV cavity was seen in diastole and apical ballooning noted during systole.

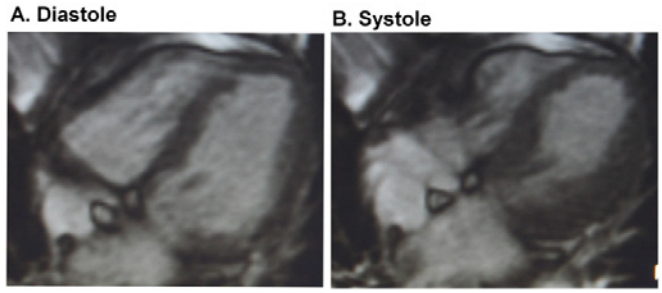

Figure 4: Serial LV ejection fraction (LVEF) monitored by echocardiography. Full normalization of LVEF occurred eight months post-discharge. Incremental doses of chemotherapy was re-instituted with 3 cycles of rituximab followed by 2 cycles of reduced R-CHOP doses (see Table 1 for specific dosing) and 3 cycles of full R-CHOP doses. R-CHOP: Rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone combination.

Cycle Number (chemotherapy re-challenge)					
	1	2	3	4	5
Rituximab (mg IV)	560	560	560	560	560
Doxorubicin (mg IV)	30	30	45	45	45
Vincristine (mg IV)	1	1	0.5	0.5	0.5
Cyclophosphamide (mg IV)	-	750	900	900	900
Prednisone (mg PO)	100 for 5days	100 for 5days	100 for 5days	100 for 5days	100 for 5days

Table 1: Chemotherapeutic regimen used during rechallenges. The slow escalation in doses is empiric since data from the literature is limited. This allowed close monitoring of cardiac function and early recognition of potential cardiac toxicity.

he diagnosis is made with pathognomonic findings of transient left entricular 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 [5]. It is estimated that TC occurs in 1 to 2% of patients presenting with an acute coronary syndrome, making this an

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 neurohormonal 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 may be difficult to gauge and may be an important confounding factor. A more intriguing possibility that we're proposing relates to the temporal sequence after her first cycle of R-CHOP which preceded her symptoms by 5 days. Chemotherapeutic agents, especially the anthracycline class such as doxorubicin, have been known to cause reversible and irreversible cardiomyopathy (for general review of chemotherapy-induced cardiotoxocity, refer to the in-depth review article by Pai and Nahata [14]. Cardiotoxicity of doxorubicin is dose-dependent and usually occurs in relation to cumulative exposure. Early cardiotoxicity peaks approximately 3 months after the last dose while late toxicity can present several years to a decade after therapy completion [15,16]. Acute LV failure after a single dose of doxorubicin is rare. Our review of literature revealed a single case of reversible LV failure following the first dose of doxorubicin in a patient with liver mass [17]. Doxorubicin has not been reported to specifically cause TC. The literature reported five cases of TC after exposure to other types of chemotherapy, i.e. bevacizumab [18], cetuximab, oxaliplatin/capecitabine combination [19], 5-flurouracil [20,21] and combretastatin [22]. There were also other sporadic cases of drug-induced TC such as with nortriptyline [23] and epinephrine [24]. Although our patient received norepinephrine infusion, it is unlikely that this has contributed to the development of TC since her symptomatology preceded the initiation of norepinephrine. This case, as far as we know, is the first reported case of a possible R-CHOP-induced TC.

Possibility for a pareneoplastic phenomenon from an occult malignancy was recently proposed by Burgdorf and associates [25]. In their report of a series of 50 patients evaluated for TC, a high incidence of malignancy was identified. The relationships between TC and their corresponding chemotherapeutic regimen however, were not detailed.

Cardiomyopathy secondary to cardiotoxic chemotherapeutic agent often results in discontinuation of the offending agent and alternative treatment is explored. In the case of TC, the risk of recurrence appears to be uncommon with isolated cases being reported [26,27]. However, more recent retrospective studies suggest that the number of recurrence may be higher, 11 [28] to19% [29]. Based on this knowledge and the limited options for our patient's progressing lymphoma, a rechallenge with R-CHOP for 5 additional cycles was undertaken. Close surveillance showed no deterioration in overall LV function and without any troponin I leak.

Conclusion

We report a case of TC presenting with syncope 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.

Support/Grant Information

National Heart, Lung and Blood Institute (HL55324, HL61610, and HL75324), Merit Review Award from the Department of Veterans Affairs and the Albert and Elizabeth Rekate Fund.

References

1. Kawai S, Kitabatake A, Tomoike H (2007) Takotsubo cardiomyopathy guidelines for diagnosis of takotsubo (ampulla) cardiomyopathy. Circ J 71: 990-992.
2. Dote K, Sato H, Tateishi H, Uchida T, Ishihara M (1991) Myocardial stunning due to simultaneous multivessel coronary spasms: a review of 5 cases. J Cardiol 21: 203-214.
3. Prasad A, Lerman A, Rihal CS (2008) Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. Am Heart J 155: 408-417.
4. Pilgrim TM, Wyss TR (2008) Takotsubo cardiomyopathy or transient left ventricular apical ballooning syndrome: A systematic review. Int J Cardiol 124: 283-292.
5. Fazio G, Barbaro G, Sutera L, Guttilla D, Pizzuto C, et al. (2008) Clinical findings of Takotsubo cardiomyopathy: results from a multicenter international study. J Cardiovasc Med 9: 239-244.
6. Seth PS, Aurigemma GP, Krasnow JM, Tighe DA, Untereker WJ, et al. (2003) A syndrome of transient left ventricular apical wall motion abnormality in the absence of coronary disease: a perspective from the United States. Cardiology 100: 61-66.
7. Virani SS, Khan AN, Mendoza CE, Ferreira AC, de Marchena E (2007) Takotsubo cardiomyopathy, or broken-heart syndrome. Tex Heart Inst J 34: 76-79.

8. Mitsuma W, Kodama M, Ito M, Tanaka K, Yanagawa T, et al. (2007) Serial electrocardiographic findings in women with Takotsubo cardiomyopathy. Am J Cardiol 100: 106-109.

9. Gianni M, Dentali F, Grandi AM, Sumner G, Hiralal R, et al. (2006) Apical ballooning syndrome or takotsubo cardiomyopathy: a systematic review. Eur Heart J 27: 1523-1529.

10. Ibáñez B, Navarro F, Farré J, Marcos-Alberca P, Orejas M, et al. (2004) Takotsubo transient left ventricular apical ballooning is associated with a left anterior descending coronary artery with a long course along the apical diaphragmatic surface of the left ventricle. Rev Esp Cardiol 57: 209-216.

11. Ibanez B, Navarro F, Cordoba M, M-Alberca P, Farre J (2005) Takot-subo transient left ventricular apical ballooning: is intravascular ultrasound the key to resolve the enigma? Heart 91: 102-104.

12. Wittstein IS, Thiemann DR, Lima JA, Baughman KL, Schulman SP, et al. (2005) Neurohumoral features of myocardial stunning due to sudden emotional stress. N Engl J Med 352: 539-548.

13. Dec GW (2005) Recognition of the apical ballooning syndrome in the United States. Circulation 111: 388-390.

14. Pai VB, Nahata MC (2000) Cardiotoxicity of chemotherapeutic agents: incidence, treatment and prevention. Drug saf 22: 263-302.

15. Shan K, Lincoff AM, Young JB (1996) Anthracycline-induced cardiotoxicity. Ann Intern Med 125: 47-58.

16. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA (1973) A clinicopathologic analysis of adriamycin cardiotoxicity. Cancer 32: 302-314.

17. Hayek ER, Speakman E, Rehmus E (2005) Acute doxorubicin cardiotoxicity. N Engl J Med 352: 2456-2457.

18. Franco TH, Khan A, Joshi V, Thomas B (2008) Takotsubo cardiomyopathy in two men receiving bevacizumab for metastatic cancer. Ther Clin Risk Manag 4: 1367-1370.

19. Kim L, Karas M, Wong SC (2008) Chemotherapy-induced takotsubo cardiomyopathy. J Invasive Cardiol 20: E338-340.

20. Kobayashi N, Hata N, Yokoyama S, Shinada T, Shirakabe A, et al. (2009) A case of takotsubo cardiomyopathy during 5-flurouracil treatment for recital adenocarcinoma. J Nippon Med Sch 76: 27-33.

21. Gianni M, Dentali F, Lonn E (2009) 5 Fluorouracil-induced apical ballooning syndrome: a case report. Blood Coagul Fibrinolysis 20: 306-308.

22. Bhakta S, Flick SM, Cooney MM, Greskovich JF, Gilkeson RC, et al. (2009) Myocardial stunning following combined modality combrestatin-based chemotherapy: two case reports and review of the literature. Clin Cardiol 32: E80-84.

23. De Roock S, Beauloye C, De Bauwer I, Vancraynest D, Gurne O, et al. (2008) Tako-tsubo syndrome following nortriptyline overdose. Clin Toxicol 46: 475-478.

24. Wong CP, Jim MH, Chan AO, Chau EM, Chow WH (2008) Iatrogenic tako-tsubo cardiomyopathy. Int J Cardiol 125: e16-18.

25. Burgdorf C, Kurowski V, Bonnemeier H, Schunkert H, Radke PW (2008) Long-term prognosis of the transient left ventricular dysfunction syndrome (Tako-Tsubo cardiomyopathy): focus on malignancies. Eur J Heart Failure 10: 1015-1019.

26. Uechi Y, Higa K (2008) Recurrent takotsubo cardiomyopathy within a short span of time in a patient with hereditary motor and sensory neuropathy. Int Med 47: 1609-1613.

27. Legriel S, Bruneel F, Dalle L, Appere-de-Vecchi C, Georges JL, et al. (2008) Recurrent takotsubo cardiomyopathy triggered by convulsive status epilepticus. Neurocrit Care 9: 118-121.

28. Elesber AA, Prasad A, Lennon RJ, Wright RS, Lerman A, et al. (2007) Four-year recurrence rate and prognosis of the apical ballooning syndrome. J Am Coll Cardiol 50: 448-452.

29. Schneider B, Desch U, Stein J (2009) Recurrence rate in patients with takotsubo cardiomyopathy during long term follow-up. Circulation 120: S891.