



[CASE REPORT]

Four Cases of Takotsubo Cardiomyopathy Linked with Exacerbations of Psychiatric Illness

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ABSTRACT

Objective. Takotsubo cardiomyopathy is a rare cardiac syndrome most often occurring in post-menopausal women after an acute episode of severe emotional or physical stress. Prior literature suggests a higher prevalence of anxiety and depression among patients with Takotsubo cardiomyopathy. We observed four cases of Takotsubo cardiomyopathy at one tertiary care center preceded by and concurrent with exacerbations of psychiatric illness rather than after acute episodes of stress. We examined each to further understand Takotsubo cardiomyopathy's pathogenesis and relationship to psychiatric illness.

Methods. We retrospectively reviewed four consecutive cases of Takotsubo cardiomyopathy at one tertiary center from August 2009 to October 2009. The *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision* criteria were used to diagnose psychiatric illness. Each patient was diagnosed with

Takotsubo cardiomyopathy via cardiac catheterization.

Results. Each woman (age range 53–67 years) was previously diagnosed with psychiatric illness. Psychiatric illnesses were as follows: Alzheimer's dementia with psychotic features, adjustment disorder, major depressive disorder, and bipolar affective disorder type 1. All four cases demonstrated exacerbations of their psychiatric illness just prior to and concurrent with their diagnosis of Takotsubo cardiomyopathy. They showed improved left ventricular ejection fraction within 1 to 3 weeks after diagnosis with supportive care.

Conclusions. Differing from the traditional cases of Takotsubo cardiomyopathy, which follow acute events of stress, our four cases indicate exacerbations of underlying psychiatric illness can lead to Takotsubo cardiomyopathy. In addition to anxiety and depression, psychosis and mania may predispose an individual to Takotsubo cardiomyopathy. We suggest that cardiologists and psychiatrists be

aware of this association and screen patients. We suggest further studies that may help better understand the connection between the heart and mind.

INTRODUCTION

Cardiac pathology is influenced by psychiatric illness. Postmyocardial infarction depression is widely researched. One in every six patients suffers depression 2 to 3 weeks after myocardial infarction.¹ Patients with postmyocardial infarction depression are at increased risk for ventricular arrhythmias.² A more recently recognized and increasingly encountered cardiac disorder, Takotsubo cardiomyopathy (TTC), may have associations with psychiatric illness.

TTC is a rare cardiac syndrome occurring almost exclusively in postmenopausal women.³ Temporary stunning of the left ventricular apex causes chest pain and myocardial injury. Importantly, cardiac catheterization does not show acute coronary occlusion. TTC represents 1.7 to 2.2 percent of suspected acute coronary syndrome. Postmenopausal women account for 82 to 100 percent of cases.⁴ Leading hypotheses attribute myocardial stunning to catecholamine excess.⁵ Interestingly, ventricular function improves 1 to 4 weeks afterwards in patients surviving the initial event.⁶

In previous research, postmenopausal women suffered acute onset chest pain in the setting of acute emotional stress (e.g., death of a loved one, divorce). A recent review described a 21-percent prevalence of anxiety and depression among patients with TTC.⁷ Patients with TTC had a seven-fold increase in the prevalence of depression and anxiety by history in a chart review.⁸ We present this series as further evidence that TTC may be more common in postmenopausal women with psychiatric illness. Similarly, psychiatric illness may be under recognized in women presenting with TTC. Our series suggests that

exacerbations of an underlying psychiatric illness could actually precipitate TTC. In addition to depression and anxiety, psychosis and mania may predispose to TTC. Better awareness of the association will identify TTC and psychiatric illness.

METHODS

We retrospectively reviewed four consecutive admissions to Johns Hopkins Hospital from August 2009 to October 2009 found to have TTC. Each patient was diagnosed with psychiatric illness based on the *Diagnostic and Statistical Manual for Mental Disorders, Fourth Edition, Text Revision* (DSM-IV) criteria.⁹ All patients were diagnosed with TTC after receiving a cardiac catheterization using the following criteria: A) dyskinesia of the apical segment of the left ventricle with regional wall motion abnormalities extending beyond the distribution of one epicardial vessel and B) luminal coronary artery obstruction of less than 50 percent. Three patients were diagnosed with TTC at our institution. One was diagnosed elsewhere and presented to our hospital for psychiatric illness. Three patients were subsequently treated on the inpatient psychiatric unit.

We recorded patient demographics and the circumstances preceding each patient's diagnosis with TTC. We report the patients' presenting symptoms, their electrocardiographic findings, and left ventricular ejection fraction at diagnosis. Each patient received an echocardiogram 1 to 3 weeks after diagnosis to screen for normalization of left ventricular ejection fraction. All patients were treated for their psychiatric illness.

CASE REPORTS

Case #1. *Dementia with psychotic features.* A 66-year-old Caucasian woman with Alzheimer's dementia was admitted for increased agitation, aggressiveness, and delusions. She was agitated and stressed by recent delusions that she

had recently delivered multiple babies and was separated from them. Although she had no cardiac symptoms, an admission electrocardiogram showed deep T-wave inversions. She was diagnosed with TTC via cardiac catheterization with a left ventricular ejection fraction (LVEF) of 30 percent. An echocardiogram nine days after the diagnosis of TTC revealed LVEF of 60 percent. She required a month-long hospitalization for stabilization of her psychiatric and cardiovascular pathology.

Case #2. *Adjustment disorder.* A 57-year-old Caucasian woman with hypertension, diabetes, and neuropathic pain suffered a common bile duct injury during a laproscopic cholecystectomy that was repaired via Roux-en-Y hepaticojejunostomy. She was discharged to rehabilitation but suffered decreased mood and decreased motivation in the months following her surgery. She presented 10 weeks after her surgery with worsening nausea, vomiting, and diarrhea as well as back pain and dyspnea. Electrocardiogram showed T-wave inversions and a prolonged QT interval. She was diagnosed with TTC via catheterization (LVEF=35%). With supportive therapy, an echocardiogram nine days after the diagnosis of TTC revealed LVEF of 55 percent.

Case #3. *Major depression.* A 53-year-old African American woman with recently diagnosed major depression was transferred from an outside hospital after taking an overdose of sleeping pills, with chest pain and T-wave inversions on electrocardiogram. She was diagnosed with TTC by cardiac catheterization (LVEF=35%). She was transferred to psychiatry stabilization for treatment of her depression with duloxetine. An echocardiogram seven days after the diagnosis of TTC revealed LVEF of 50 percent.

Case #4. *Bipolar affective disorder.* A 53-year-old African American woman with rheumatoid arthritis, asthma, and bipolar

disorder suddenly became paranoid and suspicious of police being able to see inside her house. As reported by her daughter, she was “running, talking, and agitated” for a number of days. In this setting, she developed chest pain. She presented to an outside hospital with chest pain, dyspnea, and precordial T-wave inversions

with prolonged QT interval. After cardiac catheterization, she was diagnosed with TTC (LVEF=30%). Two days after discharge, she presented to the same hospital with dyspnea and was prescribed a steroid taper for presumed asthma exacerbation. The next evening, police apprehended her walking in the street in a bathrobe with a box-cutter. She was admitted to our institution for treatment of mania, likely worsened by steroids. After a seven-day psychiatric admission, she was discharged with divalproex. Seventeen days after her diagnosis of TTC, an echocardiogram showed LVEF of 60 percent.

All four cases represent atypical presentations of TTC. In a typical presentation, a post-menopausal woman will suddenly develop chest pain after being presented with an acute physical or emotional stressor (e.g., death in the family). As exemplified in Case #1, the stress was a result of the patient’s psychosis secondary to dementia. In Case #1, her psychosis caused extreme anxiety and agitation. Prolonged stress in the setting of an adjustment disorder rather than an acute emotional event predisposed Case 2 to developing TTC. In Case 3, the patient was in the midst of severe major depression to the point of overdosing on pills. Although she had chronic stressors in the months before, her severe depression most likely caused the cascade of physiologic changes leading to TTC. After her depression was better treated, she was able to cope better with her chronic stressors. In Case 4, the patient became hyperemotional and paranoid in a manic episode that

preceded and was ongoing with her chest pain and subsequent diagnosis of TTC. Her manic paranoid state led to ongoing heightened emotional responses to otherwise benign stimuli. Along with the heightened state of the mania, her increased emotional state itself could have led to physiologic changes and TTC.

DISCUSSION

The propensity for TTC to occur in post-menopausal women and its selective apical myocardial stunning has yet to be explained. One theory suggests premenopausal women are protected from catecholamine toxicity by a negative inotropic β_2 adrenergic response.⁹ As estrogen influences the ratio of β_1 : β_2 adrenergic receptor expression, postmenopausal women have reduced β_2 adrenergic expression and less catecholamine protection. Selective activation of β_1 and β_2 receptors causes a combination of myocardial stunning and apoptosis creating the apical ballooning syndrome. Men presumably suffer diffuse myocardial damage in catecholamine excess as low estrogen favors the β_1 adrenergic response.¹⁰

Patients with psychiatric conditions may have a higher catecholamine response to stressful situations and decreased inhibition of catecholamines. Chronic stress has been shown to increase the risk of developing cardiac disease.¹¹ Stress increases circulating catecholamines resulting in more persistent physiological changes in women rather than men.¹² Anxiety-related somatic symptoms in healthy men and women are also associated with the development of coronary artery disease.¹³ Barton et al¹⁴ found that patients with major depression and comorbid panic disorder have elevated sympathetic activity apart from patients with panic disorder alone. In the same study,¹⁴ patients with major depression exhibited reduced reuptake of norepinephrine, suggesting that patients with major depression have prolonged cardiac

sympathetic stimulation. Nguyen et al¹⁰ reviewed recent publications and concluded that anxiety and panic attacks may contribute to the syndrome during acute stress.

Our four cases show exacerbations of their psychiatric illnesses just prior to and coincident with their diagnosis of TTC. In each case, the psychiatric illness seemed to be the underlying cause of the patients’ ongoing stress as well as exacerbation of any of their stressors leading to TTC. These cases suggest exacerbations of underlying psychiatric disorders could themselves result in supraphysiologic alterations in catecholamines and prolonged cardiac sympathetic stimulation that precipitates TTC. Unlike previous reports that note an association of TTC in patients with previous diagnoses of depression and anxiety, our series shows that ongoing psychiatric illness could precipitate TTC. As Barton suggests, psychiatric illness may induce higher catecholamine responses to stress and allow longer cardiac sympathetic stimulation through reduced catecholamine reuptake.¹⁴ Furthermore, two of our cases indicate that an exacerbation of another psychiatric illness, such as mania and psychosis, and its effects can lead to similar stress and physiologic changes that may precipitate TTC.

The influence of psychiatric illness in the pathogenesis of TTC may be an under-recognized association. Women treated for TTC may have undiagnosed psychiatric conditions. Mental health screening should accompany therapy for TTC. Our cases propose more questions for potential future research. A larger study where patients with TTC are separated by the presence or absence of psychiatric illness could elicit the importance of these associations. Furthermore, catecholamine levels measured in patients with and without psychiatric illness in the setting of TTC may provide further insight. Continued research may help us better

understand the connection between the heart and the mind.

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