A rare case of Takotsubo syndrome in a patient 5 months after heart transplantation

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Abstract

Takotsubo syndrome is an acute heart failure syndrome with a pathogenesis that is attributed to sympathetic stimulation. This case report describes a unique case of a 5 month heart-transplanted female patient who developed apical ballooning on an echocardiography exam performed following an emotional stress event. Detailed clinical investigations and imaging techniques confirmed the diagnosis of Takatsubo syndrome. Our case indicates that Takatsubo’s cardiomyopathy should be included in the differential diagnosis of heart-transplanted patients presenting with sudden graft dysfunction mimicking acute graft rejection or acute coronary syndrome.

Keywords Takatsubo; Broken heart syndrome; Cardiomyopathy; Heart transplantation

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Introduction

Takotsubo syndrome is an acute heart failure syndrome which shows complete recovery of contractile function in nearly all cases1,2. There is considerable evidence that sympathetic stimulation is central to the pathogenesis of the Takotsubo syndrome. Here, we present a case of a young female patient, only 5 month post heart transplantation (HTx) that was diagnosed with Takatsubo’s syndrome.

Case report

A 44-year-old female patient underwent HTx in our institution in February 2018 due to an idiopathic non-ischaemic, non-dilated cardiomyopathy. Prior to transplantation, she underwent implantation of continuous left-ventricular assist device (Heartmate 3) as a bridge to transplantation in June 2017 due to severe worsening heart failure. Our patient’s heart donor was a 39-year-old, ‘light-smoker’, premenopausal female patient that died due to a spontaneous haemorrhagic cerebral bleeding. In the months following her HTx, our patient was performing regular daily activities with no limitations, classified as New York Heart Association Functional Class 1. She was having regular menstrual periods. Her immunosuppression regimen included calcineurin inhibitor (cyclosporine), mycophenolate mofetil, and low-dose steroid therapy. Transthoracic echocardiography (TTE) exams performed by our local protocol consistently demonstrated good left ventricular (LV) systolic function with an area of septal akinesia. Haemodynamic evaluations and endomyocardial biopsies performed via right internal Jugular vein were performed routinely according to the International Society of Heart and Lung transplantation guidelines.3

Myocardial biopsy performed on 3 July 2018 was negative for acute cellular or antibody-mediated rejection as were her previous biopsies.

The patient arrived for her routine TTE exam on 25 July 2018. Surprisingly, her LV systolic function evaluation revealed moderate global dysfunction (estimated ejection fraction 40%) with regional wall motion abnormalities involving the mid-segment and distal segment of the left ventricle, mostly the apex (Supporting Information, Video S1). She
was asymptomatic with no complaints of chest pain, palpitations, or dyspnoea. However, she did describe a significant and emotional dispute with her spouse the preceding day. The differential diagnosis for our patient’s new LV dysfunction mainly included acute myocardial event, acute graft rejection, and Takotsubo syndrome. Thus, the patient was immediately admitted for further investigations. Her electrocardiogram was unremarkable. Laboratory tests results showed normal white blood cells count and mild anaemia (total leukocytes 5.00 K/μL, normal range 4.800–10.800, haemoglobin 11.3 g/dL, normal range 12–16 g/dL) and elevated creatinine (2.1 mg/dL, an increase from a baseline of 1.1 mg/dL, normal range 0.51–0.91 mg/dL). Natriuretic peptide (NT)-pro-BNP level was elevated beyond her baseline levels to a value of 2917 pg/mL, whereas cardiac troponin T was only mildly elevated, 52 ng/L (normal range 0–4 ng/L).

Her cyclosporine level was 362 ng/mL (normal range values adjusted for time post-transplantation, 150–200 ng/mL). To exclude an acute coronary event as the cause of the LV dysfunction, she was referred immediately to the catheterization laboratory; however, her coronary angiography was normal. Haemodynamic measurements via right jugular vein were in normal range, and an endomyocardial biopsy was performed. Pending the results of the myocardial biopsy, she was started on pulse steroids. On the day after her admission, the results of the myocardial biopsy revealed no sign of acute cellular or antibody-mediated graft rejection but did show evidence of interstitial fibrosis and endocardial thickening.

Following a period of 2–4 weeks cardiac biomarkers gradually returned to the patient’s baseline levels. Cardiac magnetic resonance imaging was negative for late gadolinium enhancement ruling out a possible diagnosis of myocardial infarction or acute myocarditis (Figure 2). Moreover, T2-weighted sequence demonstrated a high signal intensity in the apical segments. Accordingly, the diagnosis of Takotsubo syndrome was made in a 5 month heart-transplanted patient.

Discussion

Takotsubo syndrome, also known as transient apical ballooning or ‘broken heart syndrome’, is an acute heart failure syndrome which is frequently precipitated by a stressful event and has a clinical presentation that is indistinguishable from a myocardial infarction.1,2,5 Complete recovery of contractile function has been documented in nearly all cases.1,2 Diagnostic criteria are presented in recently published position statement and expert consensus document5 on Takotsubo syndrome, which have incorporated modifications to the Mayo Clinic criteria.1 Although the precise pathophysiological mechanisms of Takotsubo syndrome are incompletely understood, there is considerable evidence that sympathetic stimulation is central to its pathogenesis.6 Two other cases of Takotsubo syndrome in HTx patients have been previously described, both occurring almost a decade from the transplantation and in older women.7,8 Our presented case is unique for it may clinically signify a very unlikely rapid recovery of cardiac function and the potential for successful long-term outcome.

![Figure 1](Image 307x77 to 536x267) Endomyocardial biopsy specimen stained for Masson trichrome revealing interstitial fibrosis and endocardial thickening.

![Figure 2](Image 59x77 to 288x250) Cardiac magnetic resonance imaging was negative for gadolinium delayed enhancement ruling out a possible diagnosis of myocardial infarction or acute myocarditis. Sub-endocardial enhancement was evidenced in the medial septal wall most probably due to a previously known peri-implantation injury as demonstrated in prior echocardiographic exams.

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sympathetic re-innervation as early as 5 months after HTx, previously demonstrated only by iodine-123 meta iodo-benzylguanidine uptake. Alternatively, this case supports pathophysiological mechanisms other than direct neural sympythetic stimulation to the development of Takatsubo syndrome. These possible mechanisms include the effect of circulating factors including epinephrine on the transplanted heart and diffuse microvascular dysfunction. Moreover, there is a possible causation between immunosuppressive treatment and the occurrence of Takatsubo syndrome. Calcineurin inhibitors may promote epicardial endothelial dysfunction and induce direct damage to the myocardium. This, in turn, may increase the susceptibility of heart-transplanted patients for the development of Takotsubo syndrome. These possible mechanisms include the effect of pathophysiological mechanisms other than direct neural sympathetic stimulation to the development of Takatsubo syndrome. This, in turn, may increase the susceptibility of heart-transplanted patients for the development of Takotsubo syndrome. However, cyclosporine, which was used by our patient, is much less cardiotoxic than tacrolimus, thus leaving a question for his role in this specific case. Furthermore, of interest is the relative younger age of our patient and the patient’s donor, thus questioning the hypothesis that hyper-oestrogen state may have a protective role from Takotsubo syndrome.

In conclusion, we present a case of Takotsubo syndrome in a young female patient occurring early after HTx and diagnosed according to most recent criteria. Our case suggests that Takotsubo syndrome should be included in the differential diagnosis of post HTx patients presenting with sudden cardiac dysfunction mimicking acute graft rejection or acute coronary syndrome.

Conflict of interest
None declared.

Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article.

Movie S1. The patient index presentation, exam performed on July 25th showing moderate global dysfunction (estimated LV ejection fraction 40%) with regional wall motion abnormalities involving the mid- and distal segments of the LV, mostly the apex.

Movie S2. Repeated exam on July 26th, the day after her admission, showing only mildly reduced LV systolic function.

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