


Takotsubo syndrome in a heart transplant recipient with poor cardiac sympathetic reinnervation

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Abstract

Takotsubo syndrome (TTS), also referred to as stress cardiomyopathy, is characterized by transient left ventricular apical ballooning in the absence of obstructive coronary artery disease. Catecholamine-induced cardiac injury or vasospasm has been implicated in this pathophysiology. We present a case of a 67-year-old man 10 years after heart transplantation diagnosed with TTS. Sympathetic reinnervation could not be detected by iodine-123 meta iodobenzylguanidine uptake, suggesting that TTS can occur in the absence of functional sympathetic nerve systems reconstruction.

Keywords Takotsubo syndrome; Heart transplantation; Cardiac sympathetic reinnervation; ¹²³I-MIBG scintigraphy

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Introduction

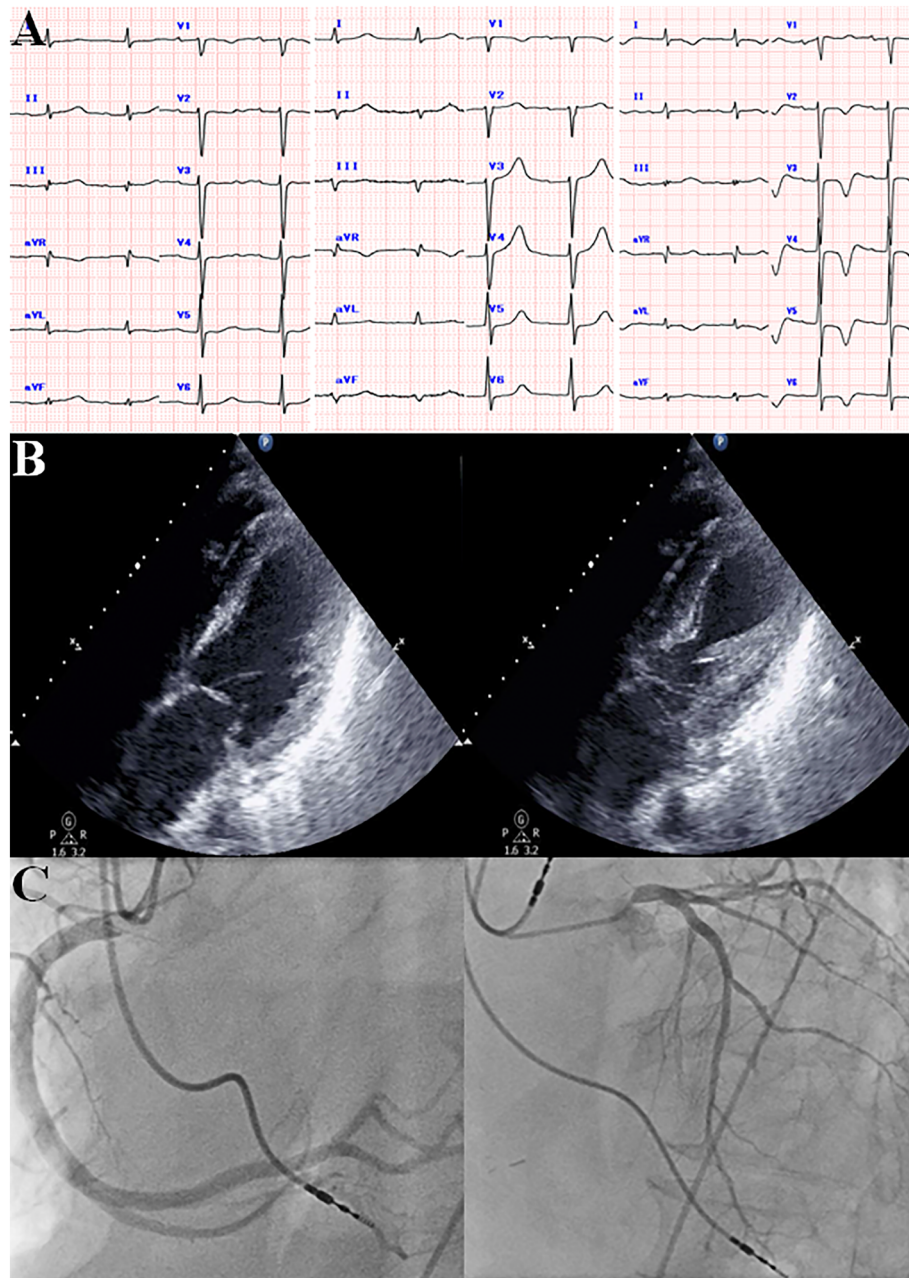
Takotsubo syndrome (TTS) is an acute cardiac dysfunction that typically represents hypokinesia of the apical segment of the left ventricle (LV) beyond a single coronary artery territory. One common feature is a surge in catecholamines in response to emotional or physical stress¹. Therefore, catecholamine-induced cardiomyocyte injury and epicardial coronary artery or microvascular spasm have been proposed for the pathophysiology.² Heart transplantation caused cardiac denervation by surgical interruption of the sympathetic and parasympathetic nerve signalling; however, cardiac reinnervation remains a matter of debate. Myocardial uptake of iodine-123 meta iodobenzylguanidine (¹²³I-MIBG) reflects sympathetic nerve function³ and is used to assess the extent of cardiac reinnervation after heart transplantation. The present case developed TTS but did not show significant myocardial uptake of ¹²³I-MIBG, suggesting that cardiac sympathetic innervation persistently disturbed.

Case report

A 67-year-old man who had undergone heart transplantation with the biatrial technique for ischaemic cardiomyopathy

10 years earlier was transferred to our hospital with dyspnoea lasting 5 days. He had been in charge of getting a nerve-fraying project done, having some problems leading a team, and therefore, under emotional and strenuous physical stress in the days before the symptom developed. After the successful heart transplantation, he was regularly followed and had no serious complications except for cryptococcal pneumonia 9 years ago and transient complete atrioventricular block requiring pacemaker implantation 2 years ago. On admission, his blood pressure was 102/60 mmHg, heart rate 87 b.p.m., and peripheral oxygen saturation 90%. A chest X-ray showed pulmonary oedema. Electrocardiogram showed sinus rhythm with decreased R wave amplitude at inferior leads and non-significant elevation of ST segment at leads V2, 3 (*Figure 1A*). Serum troponin level was elevated at 0.173 ng/mL (normal value <0.014 ng/mL, *Table 1*). Transthoracic echocardiography was remarkable for severe hypokinesia of the apical portion of the LV and hyperkinesia of the base, with an ejection fraction of 39% (*Figure 1B* and *Table 1*). Coronary angiography revealed non-obstructive coronary artery disease (*Figure 1C*). Based on these findings, he was provisionally diagnosed with myocardial infarction with non-obstructive coronary arteries (MINOCA) for which the differential diagnosis involved TTS. Endomyocardial biopsy

Figure 1 (A) Serial change in electrocardiogram at 4 months before admission (left), admission (middle), and 8 days after admission. (B) Echocardiography in a four-chamber view at end-diastole (left) and end-systole (right) showing severe hypokinesis of the middle and apical portion of the left ventricle. (C) Coronary angiography showed minor luminal irregularities.



showed mild cellular cardiac allograft rejection (The International Society for Heart and Lung Transplantation acute cellular rejection 2004 classification Grade 1R, *Figure 2A*) and cardiac magnetic resonance T2-weighted imaging did not display increased signal in the left ventricular wall (*Figure 2B*). The patient was treated with nitrate and diuretics. Dual-isotope single-photon emission computed tomography using thallium-201 chloride ($^{201}\text{TlCl}$) and iodine-123 beta-methyl-

p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP) showed mildly impaired myocardial perfusion at inferior with the concordant defect of ^{123}I -BMIPP uptake (*Figure 2C*). The serial heart-to-mediastinal ratio level of ^{123}I -MIBG showed no significant increase at the 3 months, 2, 3, 5, 7, 8, 9, and 10 years after transplantation (early/delayed heart-to-mediastinal ratio: 1.8/1.6, 1.9/1.5, 2.1/1.7, 1.9/1.5, 2.1/1.6, 1.8/1.5, 1.7/1.5, and 1.7/1.4, *Figure 3A–C*). His acute heart failure

Table 1 Temporal changes in echocardiographical parameters, laboratory data, and medications

	On admission	On the 13th day	On the 29th day
Echocardiography			
LVDd (mm)	50	47	46
LVDs (mm)	33	27	27
LVEF (%)	39.2	60.4	65.0
S' (cm/s)	6.3	7.2	7.6
E/E'	12.4	6.4	10.9
Laboratory data			
Troponin T (ng/mL)	0.173		0.02
BNP (pg/mL)	2894	409	316
Medications			
	Telmisartan 80 mg		Azosemid 30 mg
	Nifedipine 60 mg		Nifedipine 20 mg
	Atorvastatin 10 mg		Atorvastatin 10 mg
	Tacrolimus 0.8 mg		Tacrolimus 0.1 mg
	Everolimus 0.5 mg		Everolimus 0.125 mg
	Fluconazole 200 mg		Fluconazole 200 mg
	Febuxostat 20 mg		Febuxostat 20 mg
	Linagliptin 5 mg		Linagliptin 5 mg
	Levothyroxine 25 µg		Levothyroxine 25 µg
	Rabeprazole 10 mg		Rabeprazole 10 mg

Tissue Doppler imaging parameters of S' and E/E' are expressed as the average of septal and lateral measurements. BNP, B-type natriuretic peptide; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction.

improved over 2 weeks. The follow-up echocardiography in 4 weeks showed improved left ventricular function with a complete resolution of the wall motion abnormalities (*Table 1*). He received a definitive diagnosis TTS after fulfilling the recent international expert consensus's diagnostic criteria.⁴

Discussion

Takotsubo syndrome is considered as a form of MINOCA, which is a syndrome with different aetiologies, characterized by clinical evidence of myocardial infarction in the absence of obstructive coronary arteries on angiography.^{5,6} Although the distinction between TTS and other forms of MINOCA is challenging in some cases, the normalization of LV systolic function in a relatively short period confirms the diagnosis of TTS. TTS commonly occurs in a setting in which the patient is exposed to emotional or physical stress and the resultant surge in catecholamine.¹ The underlying pathophysiological mechanisms remain undetermined; however, they include catecholamine-induced cardiomyocyte injury and

microvascular spasm resulting in myocardial stunning. Heart transplantation caused extrinsic cardiac denervation by surgically interrupting the sympathetic and parasympathetic nerve fibres in the heart. Cardiac reinnervation has been shown to occur; however, it is dependent on time after transplantation and does not occur in all recipients.⁷ Early and late myocardial uptakes of MIBG reflect a distribution of the presynaptic nerves system and neuronal function, respectively, and can be used to study the extent of cardiac innervation after heart transplantation. This patient serially underwent ¹²³I-MIBG scintigraphy, but no significant myocardial uptake occurred, suggesting that global sympathetic denervation persisted after heart transplantation. In favour of this hypothesis, his chronotropic response to exercise did not significantly improve from 5 months to 2, 3, 5, 6, 7, 8, 9, and 10 years after transplantation (peak increment in heart rate with exercise: 27, 24, 42, 38, 15, 37, 18, 36, and 17 beats, respectively). Possible explanations for the development of TTS in the absence of global regenerating nerves are the following. (i) Cardiac reinnervation partially and heterogeneously might occur⁸; however, MIBG could not detect this incomplete limited reinnervation. (ii) The transplanted heart might be hypersensitive to circulating catecholamines due to the up-regulation of β-adrenergic receptors and have an effect on inotropic responses with increased susceptibility to TTS.⁹ The recent study proposed a conceptual model describing the potential mechanism responsible for the development of TTS. They reported that patients with TTS had decreased communication between brain regions associated with emotional processing and the autonomic nervous system.¹⁰ The impaired neural network communication could handle stress inappropriately and induce an excessive stimulation of the autonomic nervous system that ultimately might make patients subject to TTS. (iii) The absence of parasympathetic reinnervation could potentially lead to an exaggerated response to circulating catecholamines. In support of this hypothesis, the parasympathetic component of heart rate variability, measured by rMSSD (the square root of the mean squared differences of successive normal-to-normal intervals), did not improve from 3 months to 10 years after transplantation (9.4 and 10.2 ms, respectively, normal value 27 ± 12 ms).

Several studies suggested that stress-induced multi-vessel coronary artery spasm contributed to the pathophysiology of TTS. We could not perform an acetylcholine challenge test for coronary spasm due to chronic renal insufficiency, but we alternatively evaluated myocardial fatty acid metabolism (¹²³I-BMIPP) combined with myocardial perfusion (²⁰¹TlCl). The mismatched areas between ²⁰¹TlCl and ¹²³I-BMIPP scintigraphy reflect transient ischaemic damage or metabolically stunned myocardium. This case showed that the metabolic abnormality was not larger than that of perfusion, suggesting that post-ischaemic myocardial stunning caused by multi-vessel coronary spasm as a causative mechanism of TTS was unlikely.

Figure 2 (A) The endomyocardial biopsy specimen showed the International Society for Heart and Lung Transplantation Grade 1R rejection. (B) T2-weighted short-axis view showed an absence of increased signal in the mid-ventricular segment of the left ventricle. (C) Polar maps of dual-isotope single-photon emission computed tomography using thallium-201 chloride (upper) and iodine-123 beta-methyl-p-iodophenyl-pentadecanoic acid (^{123}I -BMIPP, lower) myocardial images showed mild hypoperfusion at inferior.

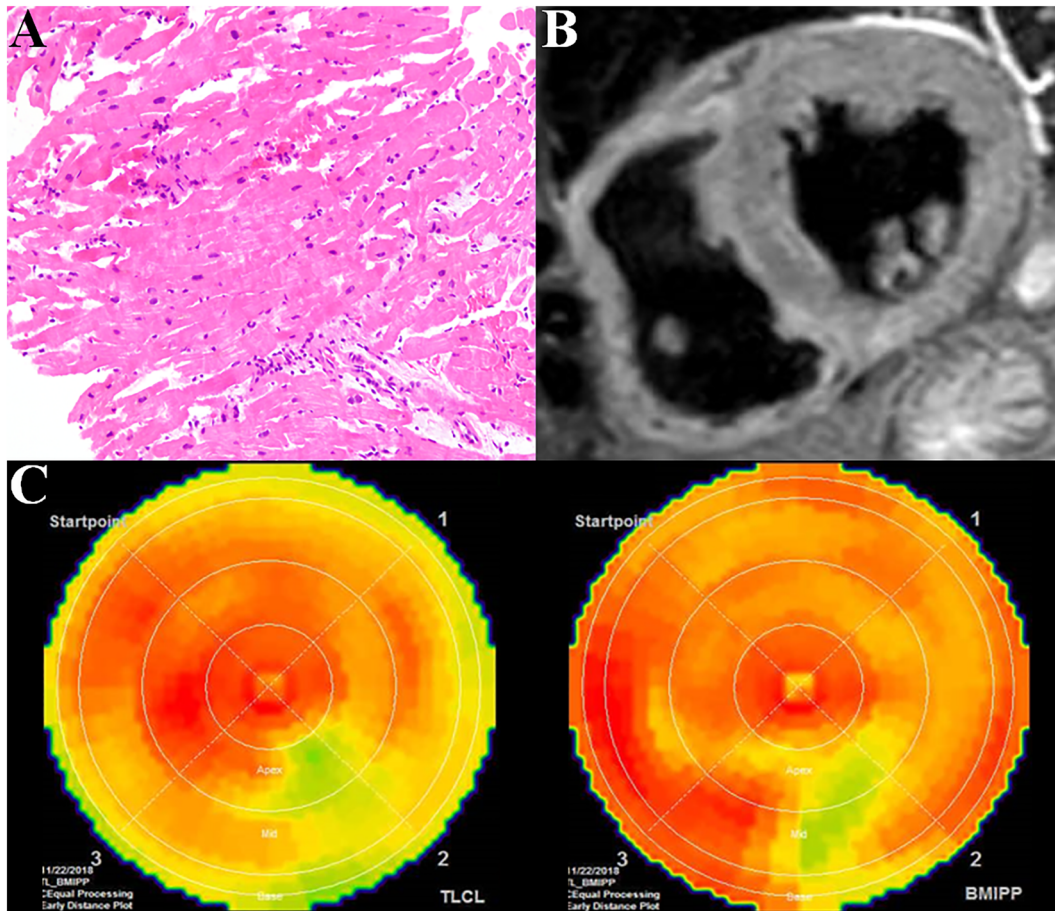
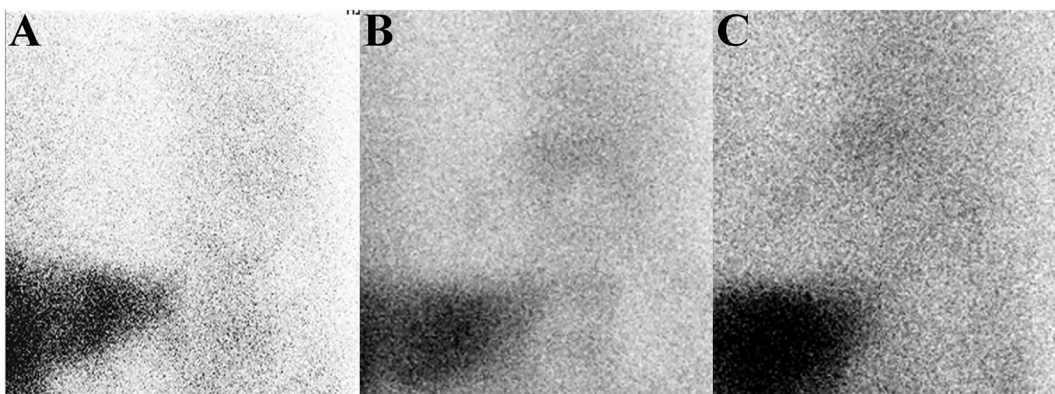


Figure 3 Early planar iodine-123 meta iodobenzylguanidine showed very low myocardial uptake at 3 months [left, heart-to-mediastinal ratio 1.75 (A)], 5 years [middle, heart-to-mediastinal ratio 1.9 (B)], and 10 years [right, heart-to-mediastinal ratio 1.73 (C)] after heart transplantation.



There are three case reports that spontaneously developed TTS after heart transplantation.^{11–13} TTS occurred 6, 9, and 10 years after heart transplantation. It is interesting to

note that all these patients including ours did not experience chest pain at the onset of TTS, suggesting the limited sensory afferent reinnervation of their hearts. Our study tried to

figure out for the first time about the mechanism of TTS by assessing the cardiac reinnervation status through serial MIBG scintigraphy, heart rate response to physical stress, and heart rate variability. The present case could underline the necessities of further studies to better understand the pathophysiology of TTS.

Takotsubo syndrome can occur in heart transplant recipients with poor sympathetic reinnervation, suggesting that complete cardiac nerve regeneration to connect between

the cardiac afferent and efferent fibres is not a prerequisite in the pathophysiology of this disease.

Conflict of interest

None declared.

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