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Takotsubo syndrome and left ventricular non-compaction cardiomyopathy: Casualty or causality?

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ABSTRACT

Takotsubo syndrome (TS) is a condition of transient regional ventricular systolic dysfunction, usually presenting with acute chest pain and/or dyspnea, that is increasingly recognized especially in post-menopausal women following a psychological or physical stress. Initially considered as a benign condition with an isolated and self-limiting episode, it is now recognized that it is associated with a significant risk of in-hospital mortality and of recurrence. We herein describe a case of a 61-year-old female with left ventricular non-compaction cardiomyopathy (LVNC) who experienced a recurrence of TS, highlighting the potential pathophysiological role for LVNC in predisposing this syndrome and its recurrence. Moreover, we underscored possible therapeutic implications deriving from this case.

1. Case report

A 61-year-old post-menopausal Caucasian female with history of anxiety, tobacco consumption, hypercholesterolemia and an episode of apical Takotsubo Syndrome (TS) in the previous six months, was brought to the emergency department because of the onset of squeezing chest pain a few hours earlier. Blood pressure was 100/60 mm Hg, temperature 35.7 °C, heart rate 76 beats per minute, respiratory rate 16 breaths per minute. She was not taking any medication. She related intense emotional stress in the days preceding admission. Cardiopulmonary examination revealed an S3 galop without signs of systemic and/or pulmonary congestion. A 12-lead electrocardiogram (ECG) showed sinus rhythm, heart rate of 61 beats per minute, QTc interval of 471 ms and deep inverted T waves involving the inferior and anterolateral leads. There were no significant ST segment deviation and/or pathological Q waves (Fig. 1). Ultra-sensitive Troponin I and N-terminal pro b-type natriuretic peptide at admission were 0.059 ng/ml (normal values < 0.04 ng/ml) and 4750 pg/ml (normal values < 150 pg/ml) respectively. The InterTAK score calculated, which takes into account clinical and diagnostic test results, was 78 with a probability of TS of 96.3% (female sex: 25 points; emotional stress: 24 points; no ST-segment depression: 12 points; acute, former or chronic psychiatric disorder: 11 points; prolonged QTc Time, female > 460 ms: 6 points). Transthoracic echocardiogram showed normal ventricular size, moderate–severe left ventricular (LV) systolic dysfunction most prominent in the mid-apical segments (ejection fraction [EF] 35%), no mitral regurgitation and/or LV outflow tract obstruction, and evidence of hypertrabeculation of the apical segments. She was admitted to the coronary care unit and urgent coronary angiography documented non-obstructed coronary arteries. The ventriculogram showed apical ballooning with regional akinesia localized to the apical segments and relative sparing of the mid-basal segments (Fig. 2A). Beta (β)-adrenergic receptor blockers, diuretics, and angiotensin converting enzyme (ACE) inhibitors were initiated with a progressive recovery of the LV systolic function during the following days, without need of inotropic support and/or evidence of arrhythmias. Seven days after the initial presentation, cardiovascular magnetic resonance (CMR) documented a global recovery of LV systolic function (EF 53%), hypokinesia of the apical segments, absence of delayed gadolinium enhancement and/or edema, and prominent trabeculation at apical segments (ratio between the thickness of the non-compacted and compacted myocardial layers in end-diastole > 2.3) (Fig. 2B) consistent with the diagnosis of LV non-compaction cardiomyopathy (LVNC) (Petersen et al., 2005; Finsterer et al., 2017). Neurological examination showed no evidence of any motor, sensory and/or coordination deficits. She denied family history of neurological or neuromuscular disorders. Patient was discharged

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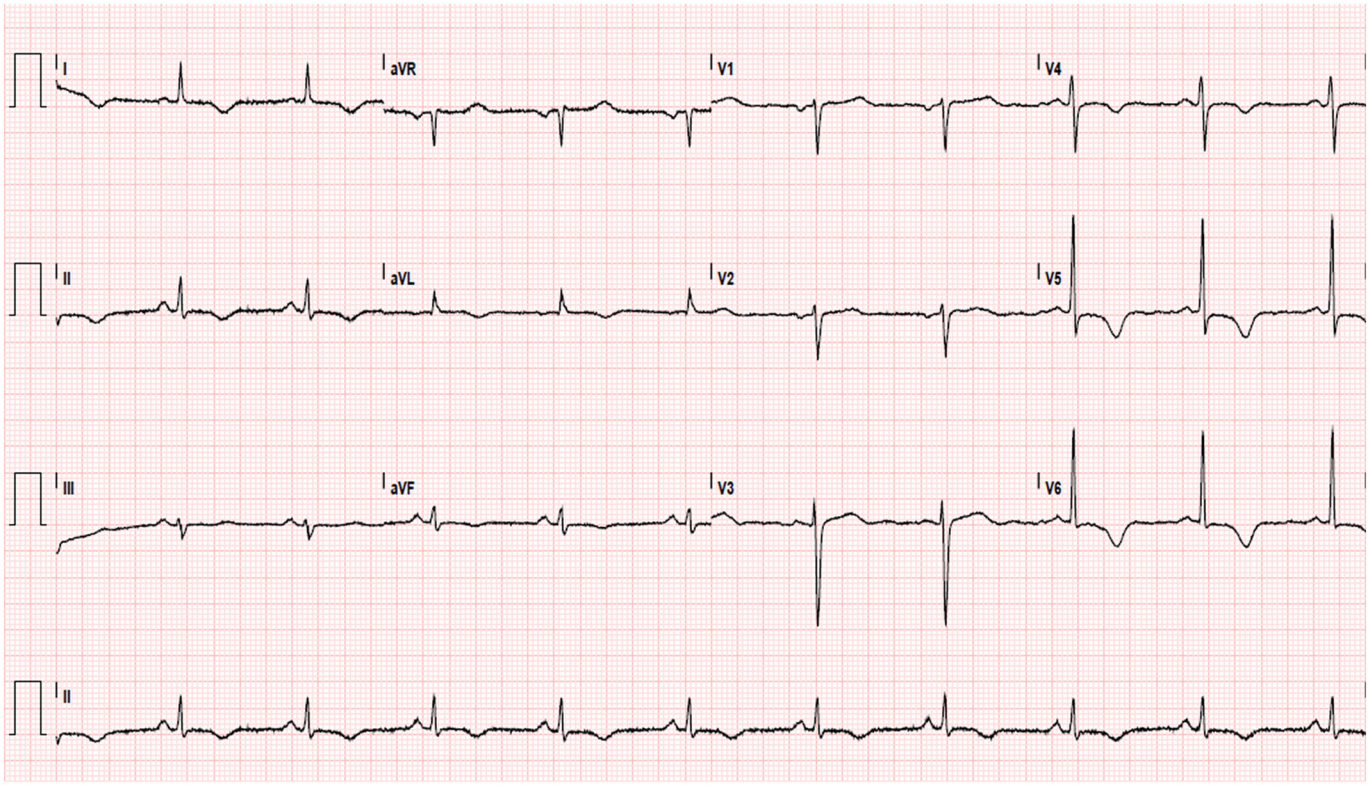

Fig. 1. ECG at presentation showed sinus rhythm, prolonged QTc interval (471 ms), deep inverted T waves in infero- and anterolateral leads.

with cardiovascular (ACE inhibitor and β-blocker) and psychiatric medications.

2. Discussion

TS, also known as stress cardiomyopathy, is a neurocardiogenic form of acute and transient regional LV myocardial dysfunction with a non-coronary artery distribution, usually affecting elderly women following the experience of an emotional or physical stress (Medina de Chazal et al., 2018). Despite the increasing awareness, it is still underdiagnosed and is estimated to represent 1–2% of patients with initially suspected acute coronary syndrome (ACS) (Medina de Chazal et al., 2018). Previously considered a benign condition due the reversibility of disease process, in-hospital mortality risk is similar to those patients presenting with ACS, with a risk of recurrence of 2–4% per patient year (Medina de Chazal et al., 2018; Templin et al., 2015). Despite the elusive pathophysiology, the brain-heart axis and neurohormonal activation are assuming a pivotal role in the pathogenesis of this syndrome (Medina de Chazal et al., 2018; Pelliccia et al., 2017). The complex neocortical and limbic integration following the interpretation of a threatening stimulus activates the neural stress response mediated by the brain stem and arcuate nucleus in the hypothalamus (Medina de Chazal et al., 2018; Pelliccia et al., 2017). This results in the abrupt release of stress-related neuropeptides stored in the pre-synaptic terminations (i.e. norepinephrine and neuropeptide Y) and circulating catecholamines at myocardial level and, through a direct catecholamine toxicity and/or an acute microvascular dysfunction, may explain the myocardial stunning (Medina de Chazal et al., 2018; Pelliccia et al., 2017; Sonnino et al., 2017). An increased sympathetic drive and conditions associated with endothelial dysfunction (i.e. diabetes, postmenopausal state, asthma) may therefore predispose to acute microvascular and myocardial dysfunction (Medina de Chazal et al., 2018).

TS has been associated with LVNC in few case reports (Table 1) (De Rosa et al., 2011; Karamitsos et al., 2008; Finsterer et al., 2013). LVNC is an uncommon form of cardiomyopathy, sporadic or familial, more prevalent in male and often described in association with neuromuscular disorders, characterized by a meshwork of interwoven myocardial strings lined with endocardium, resulting in thickened myocardium with two layers consisting of a non-compacted and a thin compacted layer of myocardium (Petersen et al., 2005; Finsterer et al., 2017). Intrauterine failure of the fetal myocardial compaction is considered only one of the potential pathophysiological mechanisms (Finsterer et al., 2017). Echocardiography is the basic tool for diagnosis, however it fails to detect LVNC in a consistent proportion of patients then confirmed with LVNC at CMR, due to suboptimal image quality, lack of uniformity accepted criteria, technical limitations and clinical setting where the test is performed (Diwadkar et al., 2017).

Whether LVNC and TS might be pathophysiologically linked remains elusive. The apical a/hypo-kinesis during TS, may more easily unmask the appearance of hyper-trabeculated myocardium and increase the diagnostic power. However, in patients with LVNC the subverted myocardial architecture has been associated with coronary microvascular dysfunction and impaired coronary flow reserve (Jenni et al., 2002), therefore potentially facilitating the occurrence (and recurrence) of TS in predisposed individuals in response to emotional or physical stress (Medina de Chazal et al., 2018; Finsterer et al., 2013; Galiuto et al., 2010). Additionally, heart rate variability has been reported to be impaired in adults with LVNC, suggesting a vagal withdrawal or sympathetic enhancement (Kawasaki et al., 2005).

In the absence of randomized studies, long-term treatment of TS remains empirical and retrospective data showed that ACE inhibitors and angiotensin-receptor blockers were associated with a lower incidence of recurrence (Singh et al., 2014). Unexpectedly, no benefit was observed with β-blockers use (Singh et al., 2014) despite their potential therapeutic effects in conditions of increased sympathetic tone, in anxiety and in the context of coronary microvascular dysfunction. Currently, no pharmacological treatments are recommended in asymptomatic patients with LVNC and without LV dysfunction or dilatation. As similarly reported by Finsterer et al. (2013), TS may recur in patients with LVNC because of the predisposing substrate of chronic coronary

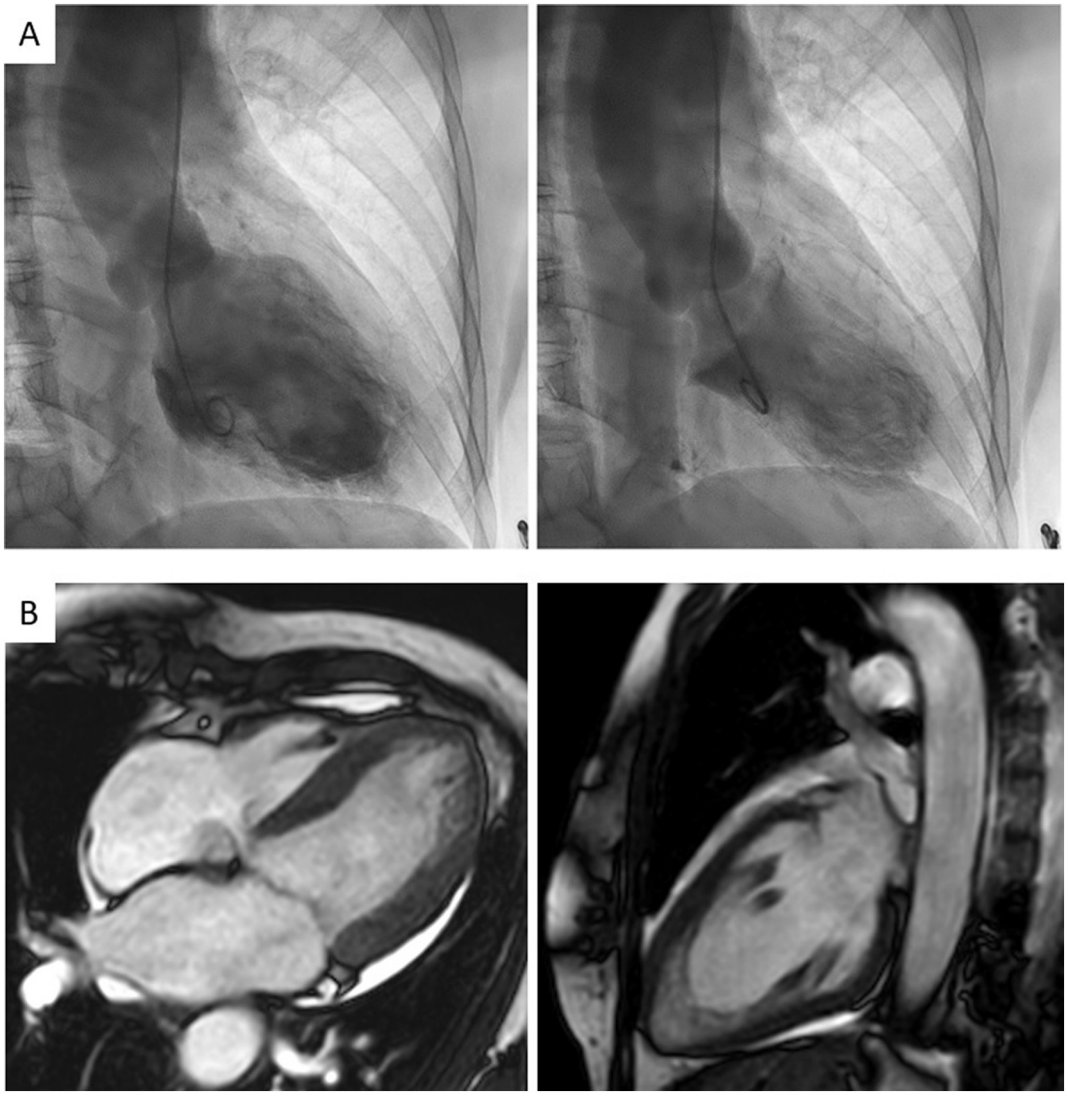

Fig. 2. Left ventriculography showed the typical apical ballooning in end-systole (Panel A). CMR performed during the recovery phase confirmed the apical hypertrabeculation with a maximum end-diastolic non-compacted to compacted myocardial thickness ratio of 2.7 (> 2.3) (Panel B).

Table 1
Clinical characteristics of patients presenting with TS and underlying LVNC.

	Case 1 Finsterer et al. (2013)	Case 2 Karamitsos et al. (2008)	Case 3 De Rosa et al. (2011)	Case 4 Del Buono MG, et al.
Age (years)	47	76	12	61
Race	Caucasian	–	–	Caucasian
Sex	Female	Female	Female	Female
Takotsubo				
Diagnostic modality	Trans-esophageal echocardiography	Ventriculography	Trans-thoracic echocardiography	Ventriculography
Pattern	Apical	Apical	Apical	Apical
Trigger	Physical (post-surgery)	–	Physical (intracranial astrocytoma with hypertensive hydrocephalus)	Emotional
Clinical presentation	Cardiac arrest due to ventricular fibrillation	Chest pain	Respiratory arrest and pulmonary edema	Chest pain
Complications	Ventricular arrhythmias	–	Ventricular arrhythmias and cardiogenic shock	No
Recurrent episodes	Yes, 10 months later (presenting with chest pain and dyspnea)	–	–	Yes, 8 months later (presenting with chest pain)
LVNC				
Areas of hypertrabeculation	Apical	Mid-ventricular and apical	Mid-ventricular and apical	Apical segments
Diagnostic modality	Trans-esophageal echocardiography	CMR	CMR	CMR
Neuromuscular disorder	Yes (myotonic dystrophy type 1)	–	–	No

Abbreviations: CMR: cardiac magnetic resonance; LVNC: left ventricular non-compaction cardiomyopathy.

microvascular dysfunction and sympathetic overdrive. Therefore, in patients with LVNC, long term treatment with ACE inhibitors and β-blockers, after the first episode of TS, might be useful to prevent its recurrence. It is worth noting that in the case reviewed ACE inhibitors and β-blockers were stopped six-months after the first episode of TS. Whether β-blockers and/or ACE inhibitors could have prevented recurrence of TS is unknown.

Finally, this patient experienced a recurrent episode of TS likely related to the persistence of the untreated underlying psychiatric illness. This may contribute to the risk of recurrence and long-term outcomes of this syndrome (Medina de Chazal et al., 2018; Templin et al., 2015), therefore requiring special attention and an integrated assessment and care involving different providers.

In conclusion, our report supports the potential of role of LVNC related myocardial structural and functional changes predisposing to TS, and the need of an individualized pharmacological approach for these patients. Further efforts are warranted to elucidate the mechanisms underlying TS and LVNC, their potential causative relation and possible therapeutic implications.

Conflict of interest and sources of funding

None declared.

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