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Takotsubo Cardiomyopathy Mimicking Myocardial Infarction in a Man with Myasthenic Crisis: A Case Report and Literature Review

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Abstract Takotsubo Cardiomyopathy is a syndrome characterized by transient and reversible regional myocardial dysfunction in the absence of obstructive coronary artery disease classically resulting in ventricular apical ballooning. It has a strong female predominance with onset generally in seventh decade of life, with hypothesized pathophysiology related to excess of catecholaminergic stimulation, particularly during episodes of physical or emotional stress. Takotsubo cardiomyopathy has been previously reported during myasthenic crisis, the acute deterioration of myasthenia gravis typically involving respiratory failure that is also associated with physical or emotional stress. We present the case of an atypically young male patient with classical takotsubo cardiomyopathy in the setting of myasthenic crisis after thymectomy initially concerning for ST segment elevation myocardial infarction, and a review of the literature of takotsubo cardiomyopathy in myasthenic crisis.

Keywords: *myasthenic crisis, takotsubo cardiomyopathy, male, thymectomy*

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1. Introduction

Takotsubo Cardiomyopathy (TC), also referred to as "broken-heart" syndrome and "stress cardiomyopathy", is a syndrome characterized by transient and reversible regional myocardial dysfunction with various patterns of regional hyperkinesis and hypokinesis in the absence of underlying obstructive coronary artery disease (CAD), most classically with left ventricular (LV) apical hypokinesis and basal hyperkinesis resulting in apical ballooning [1,2]. TC has been shown to have an overwhelming female predominance and average age of onset of 66, with strong temporal associations to emotional and physical stress, with postulated mechanisms centered around catecholamine-induced myocardial injury and catecholamine-mediated vascular spasm and dysfunction causing myocardial stunning [3,4]. TC is among the most commonly reported cardiac manifestations of Myasthenia Gravis (MG), a neuromuscular autoimmune disease with auto-antibodies to nicotinic acetylcholine receptors (anti-AChR) primarily affecting younger women and older men [5]. TC associated with MG most prominently appears during myasthenic crisis (MC), an acute deterioration of MG typically brought on by a physical or emotional stressor that usually involves respiratory muscles resulting in respiratory failure and the need for mechanical ventilation [6]. Previous reports of MC triggered TC demonstrate a female predominance with variable antecedent history of thymectomy [6]. We present the first reported case of TC in MC in a male patient after thymectomy.

2. Case Report

A 49-year-old male with a past medical history significant for MG with thymectomy 5 months prior to presentation was transferred to our institution after presenting to an outside hospital with impending respiratory failure concerning for acute MC. At the outside hospital, the patient was intubated, and started on pyridostigmine, prednisone, and intravenous immunoglobulin (IVIg). Compared to baseline EKG (Figure 1), on day 3 of his hospitalization, electrocardiogram (EKG) revealed new T wave inversions V2-V6 and inferior limb leads II, III, aVF (Figure 2).

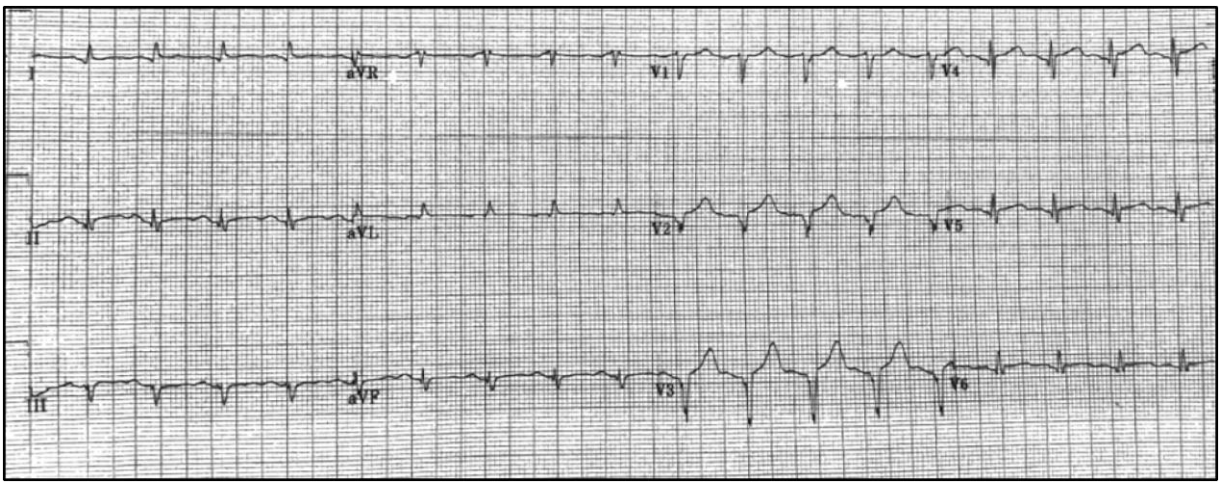

Figure 1. EKG at initial presentation. No anterolateral T-wave abnormality noted. The EKG reveals normal sinus rhythm, Q-waves in V1-V3 and T wave flattening in I and aVL

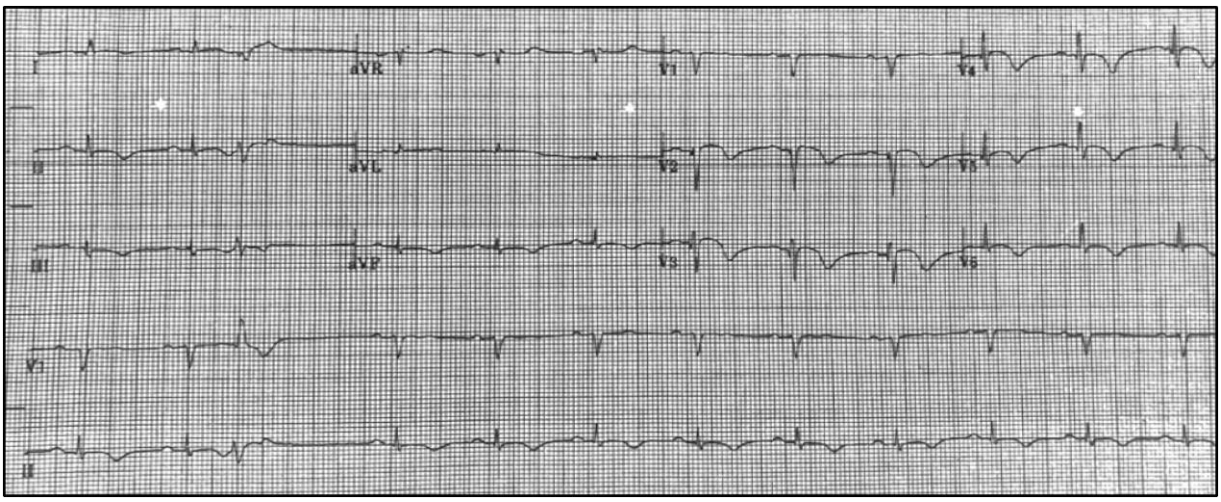

Figure 2. Subsequently obtained EKG revealing T wave inversions in precordial leads V2-V6 and inferior limb leads II, III, aVF

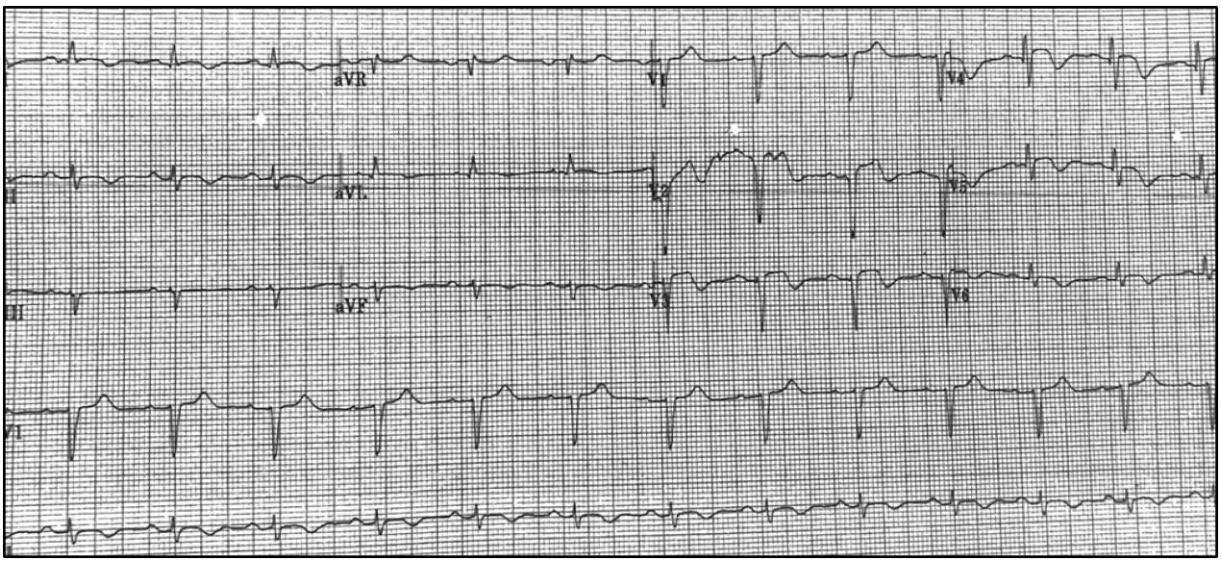

Figure 3. EKG revealing ST elevation in precordial leads (V2-V6).

Given concern for NSTEMI, intravenous heparin was started. The patient subsequently became hypotensive and was started on norepinephrine and then transitioned to phenylephrine due to tachycardia. Serial EKGs revealed mrore pronounced ST elevation in V2-V6 concerning for injury with persistent T waves inversions in inferior and precordial leads (Figure 3). Troponin levels uptrended, peaking at 2.47 (ng/mL). The Patient was transferred to our institution for emergent cardiac catheterization for suspected STEMI.

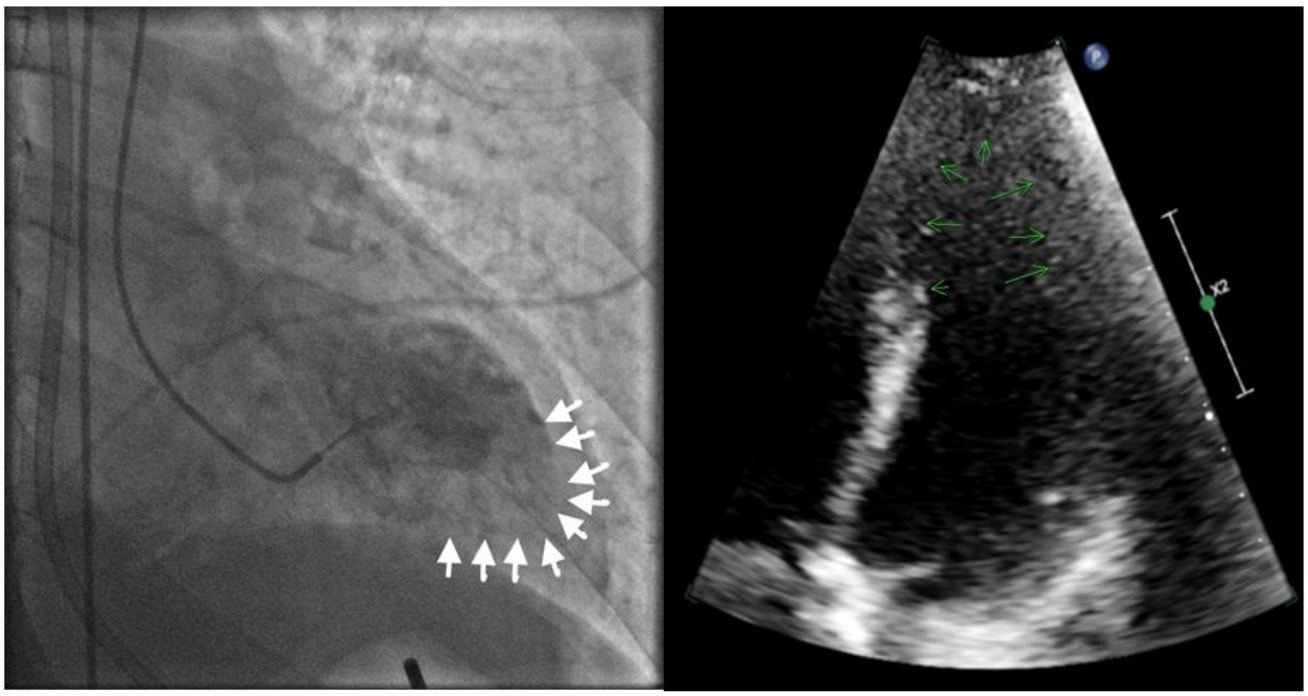

Figure 4. a (left): Ventriculogram revealing apical ballooning, b (right): TTE revealing hypokinesis of mid-distal anteroseptal, mid-apical, inferior, apex and lateral walls with apical ballooning.

Upon arrival, coronary angioprahy revealed widely patent coronaries with mild lumen abnormalities, an EF of 30 to 35% with severe hypokinesis and ballooning of the distal anterolateral/apical/inferior walls, suggestive of TC (Figure 4a). Transthoracic echocardiography (TTE) revealed severe hypokinesis of the apex along with the mid-distal anteroseptal, mid-apical, lateral and inferor walls with adequate contraction appreciated in the basal portions of the LV, consistent with TC (Figure 4b). Phenylephrine was titrated off and the patient remained stable without pressor support. IVIg, pyridostigmine, and prednisone were continued. Mechanical ventilation was continued with frequent suctioning for copious secretions perhaps exacerbated by pyridostigmine with monitoring of negative inspiratory force and forced vital capacity. The patient remained hemodynamically stable without overt signs of symptoms of acute decompensated heart failure, and was transferred back to the referring hospital for continued care. Decompensated heart failure did develop later however, was treated, and the patient was successfully extubated.

3. Discussion

TC in the setting of MC has been attributed to adverse catecholaminergic associated with the severe stress precipitated by MC, and to the temporal relationship that has been extensively documented between physical or emotional stress, the onset of TC and the reversibility of TC with resolution of antecedent stressor.

While no specific pathophysiological mechanism of TC has been elucidated, evidence points to the role of excessive sympathetic and catecholaminergic stimulation given the robust temporal association with emotional or physical precipitant events, association with conditions of catecholaminergic excess like pheochromocytoma, and the ballooning patterns seen on cardiac imaging after intravenous infusion of catecholamines and beta-agonists [7]. Four different morphologies of TC have been described; the classical type featuring apical ballooning with basal hyperkinesis; the mid-ventricular type featuring basal hyperkinesis with mid-ventricular hypokinesis and normal to hyperkinetic apex; the basal or inverted type featuring basal and mid-ventricular hypokinesis with apical hyperkinesis; the focal type featuring hypokinesis of a focal myocardial segment [8].

The distribution of hypo- and hyper-kinetic myocardium in the setting of increased adrenergic stimulation raises the question of potential regional catecholamine-mediated effects on myocardium and coronary circulation. Beta adrenergic receptors (ßAR), the G-protein coupled adrenergic receptors of the sympathetic nervous system, and sympathetic nerve endings are unequally distributed in human hearts, with a prominent apical-basal gradient containing a decreasing density of sympathetic nerve endings in the apical myocardium as compared to basilar myocardium, and increasing density of ßAR in the apical myocardium as compared to basilar myocardium [9,10]. The discrepant ratio of sympathetic nerve ending densities, and thus norepinephrine, and beta receptors in the basal and apical myocardium results in increased activity of circulating epinephrine on ßAR in the apical myocardium [11]. High concentrations of epinephrine have been shown to induce ß2AR to switch its G-protein coupling from stimulatory G-protein (Gs) to inhibitory G-protein (Gi), known as ligand-directed trafficking or biased agonism [12]. Paur et al. demonstrated in a rat model that high dose epinephrine infusion mimicking the catecholamine response to acute stress generated the classical reversible apical ballooning pattern of TC from apical and mid-ventricular hypokinesis with preserved to enhanced basal contractility, but such myocardial contractility patterns were not reproduced with equivalent high dose

norepinephrine acute stress bolus [13]. Furthermore, it was demonstrated that there is basal-apical gradient of catecholamine responsiveness to ßAR subtype, with apical cardiomyocytes having a higher density of ß2AR and greater ß2AR-induced sensitivity compared with basal cardiomyocytes [13].

Confounding the catecholaminergic-mediated myocardial dysfunction of TC are the catecholamine-mediated changes in coronary vascular tone and the parasympathetic dysfunction seen in MC. The autonomic changes of MC are characterized by parasympathetic dysfunction, with lowered parasympathetic excitatory postsynaptic potentials suspected to be secondary to damage and blockade from the nicotinic anti-AChR on postsynaptic ganglion AChR [14,15]. Elevated circulating levels of catecholamines from the physical stress of MC compounded with blunted parasympathetic innervation enables dramatic sympathetic and adrenergic tone on the coronary vasculature, both on the epicardial vessels and microcirculatory system. Reversible coronary epicardial and microcirculatory dysfunction has been confirmed in TC with transient improvements in regional myocardial dysfunction, wall motion score index, wall motion defect length, LV end systolic volume (LVESV) and EF with coronary vasodilation from infusion of ACh or adenosine [16,17].

To the best of our knowledge, this is the first case of TC in MC in a male patient after thymectomy. TC in MC has been previously reported [18-35], however there are only three previous reports of male patients with TC in MC [19,23,32], and there are only two previous reports of TC in MC after thymectomy, with both patients being female [21,30]. Review of the literature demonstrats a strong female predominance (16: 3), with an average age of onset of 64 years of age, considerably older than our patient. Demographic and LV function data from previous case reports are summarized below in Table 1. EKG changes seen in previous cases of TC during MC demonstrate a varying pattern of ST segment elevations and/or T wave inversions, most prominently in the precordial leads, most specifically the anterolateral leads. In the case of our patient, ST segment elevation followed T wave inversion. Previous analysis of EKG evolution in patients with TC show distinct patterns of evolution, with T wave inversions generally following resolution of antecedent ST elevation, and initial T wave inversion accompanied by QT prolongation without concurrent ST elevation [36]. Our case displayed initial EKG changes of T wave inversions, followed by ST elevation, and persistence of T wave inversions after resolution of ST elevation.

Table 1. Previously published cases of Takotsubo cardiomyopathy in patients with myasthenia crisis

Year, Case	Age (years)	Gender	Thymoma/ Thymectomy	TTE
2004, Arai et al. [18]	83	F	None	Extensive akinesis - apex
2005, Sousa et al. [19]	64	M	None	Dyskinesis - apex Akinesis - middle segments of all wall Hypokinesis - anterior and septal basal wall segments
2008, Hirose et al. [20]	63	F	None	LV wall motion asynergy
2009, Sasidharan et al. [21]	40	F	Thymectomy	Dilated LV, severe LV dysfunction Akinesis - apical segments Hyperkinesis - basal segments
2010, Beydoun et al. [22]	60	F	None	LVEF 32% Ballooning - apex Hyperdynamic - proximal apex*
2011, Bansal et al. [23]	77	M	None	Severe & diffusely decreased LV function, regional variations Hypokinesis - distal > proximal segments
2011, Gautiera et al. [24]	82	F	-	Dyskinesis - antero-medium & late-medium-high walls Enhancement - late postero-basal enhancement EF of 56% with conserved global kinetics**
2012, Wong et al. [25]	64	F	-	Impaired LV with EF of 30% Ballooning - apex Hyperkinesis - basal region *
2012, Nishinarita et al. [26]	52	F	Thymoma	Akinesis - apex Hyperkinesis - proximal
2012, Mayor-Gomez et al. [27]	83	F	-	Dyskinesis - apex
2013, Valbusa et al. [28]	75	F	None	Ballooning - apex Impaired LV function Mild MR and AR
2013, Anand et al. [29]	50	F	None	Hypokinesis - anterior & distal septum, apex
2014, Thanaviratananich et al. [30]	42	F	Thymectomy	Severe hypokinesis - global w/relative sparing of apex LVEF of 15%
2014, John et al. [31]	34	F	None	Hyperkinesis - apex Akinesis - basal wall
2015, Harries et al. [32]	70	M	None	Hypokinesis - apex Preserved - basal segment
2016, Cuevas et al. [33]	69	F	None	Hypokinesis - antero-/infero-apical Hyperkinesis - basal segment*
2017, Battineni et al. [34]	69	F	None	Mid-ventricular variant TC Reduced EF of 25%
2018, Jolly et al. [35]	75	F	None	Hypokinesis - apex and septal segments LVEF of 35%

Key: *Ventriculogram findings. **Cardiac MRI findings. F = Female. M = Male.

In summary, we present the case of a male patient with TC in the setting of MC after thymectomy. TC remains a rare complication of MG and MC and is uncommon in male patients and those with a history of thymectomy. Considering the prominent role of catecholamines and the asymmetric adrenergic stimulation underlying the pathophysiology of TC, understanding the overlap between MG anti-AChR and the blunted parasympathetic stimulation present in MG could serve as a potential area of investigation into the mechanism of TC in MC.

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