Nonapical Tako-tsubo Cardiomyopathy Associated with Coronary Slow Flow: A Case Report and Review of the Literature

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ABSTRACT

The exact pathophysiology of tako-tsubo cardiomyopathy (TTC) is unclear. A nonapical form of TTC precipitated by emotional stress is presented. Findings on 12 lead ECG and coronary angiogram are discussed. The role of specialized investigations such as cardiac MRI and tissue Doppler imaging are reviewed. We then examine the probable molecular explanations for this condition and suggest a probable molecular mechanism based on animal studies. Future therapeutic options are also briefly discussed.

Key words: tako-tsubo cardiomyopathy, cardiac MRI, coronary slow flow, microvascular dysfunction, ryanodine receptor 2

Case Report

A 48-year-old female patient with a 2 h history of sharp central chest pain (8/10 in intensity) radiating to her left arm and back was admitted via the emergency department. Her symptoms were triggered by emotional stress following a domestic disturbance involving her neighbor. On arrival the patient was diaphoretic, but hemodynamically stable with no evidence of heart failure. The pain subsequently improved following administration of aspirin, glyceryl trinitrate (GTN), oxygen, and repeated 5 mg doses of intravenous morphine. Coronary risk factors included occasional smoking (<10 cigarettes/wk) and a positive family history (father and paternal grandfather had both died of myocardial infarction in their mid 60 s). Comorbidities included irritable bowel syndrome, urinary stress incontinence, and a 5 y history of epilepsy following a traffic accident.

Serial ECGs following admission demonstrated sinus rhythm with initially prolonged QTc (479 ms) and dynamic ST-T changes with progressive T-wave inversion in the anterior chest wall leads (Figure 1). A 12 h troponin I level was raised to 1.87 µg/L 24 h later, the patient underwent coronary angiography. Epicardial coronary arteries were entirely unobstructed (Figure 2A,B). However marked "slow flow" was noted in the left coronary system. Interestingly, her left ventricle (LV) angiogram revealed a dilated LV cavity with marked hypokinesis of the mid LV wall segment and apparent "apical ballooning." However on closer inspection the true apex was spared and the basal LV segments were hyperdynamic (Figure 2C,D). She had mild to moderate LV impairment (ejection fraction

[EF] 42%, left ventricular end-diastolic volume [LVEDV] 119 ml, left ventricular end-systolic volume [LVESV] 69 ml). Echocardiographic reassessment the following day revealed a biplane EF of 50% (LVEDV 116 ml). An MRI was performed on the fourth day of admission to assess wall motion anomalies and myocardial scarring. A band-like area of hypocontractility of the LV mid-cavity segments with concomitant reduced signal intensity (EF 53%) was noted. Absence of late enhancement on gadolinium imaging ruled out myocarditis and scarring from myocardial infarction (Figure 3A,B). A working diagnosis of nonapical tako-tsubo cardiomyopathy was postulated and the patient was initiated on aspirin, bisoprolol, and ramipril. She was discharged with plans for clinical and echocardiographic follow-up. The repeat transthoracic echocardiogram 38 d following the index admission demonstrated entirely normal systolic and diastolic function (EF 66%, LVEDV 115 ml, LVESV 39 ml) as well as tissue Doppler velocities (Figure 4). Her QTc had normalized and the patient had regained her normal quality of life.

Discussion

The presented case unifies almost all the classical features described in stress induced myocardial stunning, frequently referred to as tako-tsubo cardiomyopathy (TTC).

Patients with TTC are predominantly female (>90%) of post menopausal age and are less likely to have "classical" risk factors for coronary disease.¹ The clinical presentation of TTC closely resembles an acute coronary syndrome. The frequently observed clinical precipitant of emotional stress and the presence of elevated plasma catecholamine levels

Figure 1. 12 lead ECG. Prolonged QTc and widespread T-wave inversion. Also note the poor R-wave amplitude in leads V1 through V3.

Figure 2. Coronary angiogram. 2A and 2B: normal right and left epicardial coronary arteries respectively. 2C and 2D: end-diastolic and end-systolic frames of the LV contrast study. The dotted black circle indicates the normokinetic true LV apex.

imply sympathetic stimulation as the culprit in TTC. This is also supported by instances of TTC following exercise testing² and dobutamine infusion.³ Although initial reports

indicated a selective dysfunction of the apex of the left ventricle, it is now accepted that transient dysfunction can also affect nonapical regions¹ (as in our patient) as well as the right ventricle.⁴

Investigations are aimed at excluding coexistent coronary artery disease and monitoring left ventricular function. The ECG is characterized by widespread ST-T wave changes with deep precordial T-wave inversion and frequently associated with QTc prolongation. There is usually a stark discrepancy between the minor elevation in cardiac biomarkers and the extensive wall motion abnormalities seen in TTC (unrelated to a particular coronary territory as seen in our patient). The absence of significant epicardial coronary artery disease should be considered a prerequisite for the diagnosis.⁵ The frequent observation of coronary "slow flow" on angiography has been substantiated by increased TIMI frame counts and impaired myocardial blush grade on fluoroscopy,¹ as well as a reduction in diastolic deceleration time and coronary flow velocity reserve on intracoronary Doppler,⁶ suggesting the possibility of microvascular dysfunction. I-123 metaiodobenzylguanidine (MIBG) scintigraphy shows a reversibly reduced uptake in the acute phase which indicates a sympathetic innervation defect.⁷ A characteristic feature on MRI is the lack of delayed hyper-enhancement following gadolinium injection which helps to differentiate TTC from myocardial infarction and myocarditis.⁸ Treatment is mainly supportive. The majority

(A)

(B)

Figure 3. Post gadolinium MRI. 3A: vertical long axis and 3B: short axis views demonstrate the absence of late enhancement after gadolinium characteristic of tako-tsubo cardiomyopathy.

Figure 4. Tissue Doppler — lateral mitral valve annulus. Normal TDI trace on follow-up echocardiography denotes full recovery of LV function.

of patients recover their LV function and have a good long-term prognosis.⁹ Beta-blocker therapy may help to prevent recurrence.¹⁰

Underlying molecular mechanisms in TTC have been suggested by a recent in vivo and in vitro study in mice;¹¹ following beta adrenergic stimulation of myocytes by

isoprenaline, cardiac myocytes suffered hypercontracture injury due to calcium overload mediated by hyperphosphorylation of ryanodine receptor 2 (RyR2). Echocardiographic parameters suggested a transient decline in left ventricular function which recovered completely by day 6. The observations in this study closely follow the features of TTC. Also of clinical interest is the observation that a benzothiazepine derivative, JTV519 (but not diltiazem) significantly limited the extent of myocyte injury by stabilizing RyR2.^{11,12} This agent may be of therapeutic benefit in the future for patients with TTC.

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