Possible pathogenesis clue of Takotsubo syndrome: a case report.

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Abstract

Takotsubo syndrome (TTS) pathogenesis remains poorly understood despite advances in research. A 66-year-old woman was admitted with a diagnosis of typical TTS. Given her 3-months follow-up, clinically stabled, we found evidence of microcirculatory disturbances and a possible clue to the abnormal lipid metabolism in TTS patients.

Keywords:
Takotsubo syndrome, reversible, microcirculatory disturbance, lipid metabolism, lipid deposition, case report

Abbreviations:
CMR = Cardiac magnetic resonance
ECG = electrocardiogram
ECV = extracellular volume
GLS = global longitudinal strain
GRS = global radial strain
LGE = late gadolinium enhancement
LV = left ventricle
TTE = transthoracic echocardiography
TTS = Takotsubo syndrome
TWI = T wave inversion

Introduction:

Takotsubo syndrome (TTS) is a type of highly heterogeneous non-ischemic cardiomyopathy and is characterized by transient wall motion abnormalities that extend beyond the territory of a single coronary artery. Despite advances in research, its pathogenesis remains incompletely understood. According to the International Takotsubo (Inter-TAK Diagnostic Criteria), we report a patient with typical TTS, and the pathophysiological processes.

History of Presentation:

A 66-year-old woman presented with sudden fatigue while climbing stairs accompanied by palpitations and dizziness four days before and was admitted to our hospital without significant relief. On admission, her
body temperature was 36.0, blood pressure measured 138/90 mmHg, heart rate was 88 beats per minute, respiratory rate was 18 times per minute, O₂ saturation was 96%, and physical examination revealed no obvious abnormalities. She denied any emotional or physical stress or family history. The electrocardiogram (ECG) showed sinus rhythm, ST-segment elevation and a positive-negative biphasic T-wave in leads II, III, aVF, V3 and V4, T-wave inversion in lead V5-V6, accompanied by a prolonged QTc interval of 516 ms (Figure 1A). Abnormal laboratory findings on admission included elevated N-terminal pro-brain natriuretic peptide of 3990.0 pg/ml (normal range: 0-125 pg/ml), Troponin I of 1.3 μg/L (normal range: 0-0.0229 μg/L) and decreased serum potassium of 3.2 mmol/L (normal range: 3.5-5.5 mmol/L). A computed tomography scan of the chest showed an enlarged cardiac contour and a small amount of pleural effusion.

**Past Medical History**

She had a long medical history of hypertension and gastritis, which were well controlled.

**Differential Diagnosis**

The patient’s clinical presentations were not typical, but biochemical findings and ECG results were referred to Acute Coronary Syndrome and Acute Heart Failure.

**Investigations**

On hospital day 4, a transthoracic echocardiography (TTE) showed apical hypokinesis and basal hypercontractility of the left ventricle (LV) (Figure 2A and B). Coronary angiography was performed at 16:00 on the same day and showed no obstructive coronary artery lesions (Figure 3). A presumptive diagnosis of apical type TTS was therefore made and treatment was adjusted accordingly. Cardiac magnetic resonance (CMR) (supplementary material for CMR parameters) was performed at 21:20 on the seventh day of admission to further characterize the myocardium. CMR showed generalized LV apical dyskinesia with a reduced left ventricular ejection fraction of 43% and reduced LV global longitudinal strain (GLS)(-9.8%), global circumferential strain (GCS)(-12.7%) and global radial strain (GRS) rates (19.41%) (The normal reference ranges of LV GLS, GRS and GCS are -21.6(-17.4, 25.8),59.3(38.3, 80.3%) and -24.3(-19.1, 29.5%)²) (Figure 4A-C) and mild late gadolinium enhancement (LGE) on LV apical anterior and inferior wall (Figure 4G.H) without visible edema on STIR BB Triple IR sequence (myocardial edema ratio was defined as the ratio between myocardial signal intensity (SI) to skeletal muscle SI, and myocardial edema ratio [?1.9 represented edema³]. Interestingly, decreased myocardial perfusion was found in the anterior, lateral, inferior and infero-septal walls of the apical LV on resting first-pass perfusion imaging (Figure 4I) and myocardial T1 mapping and T2 mapping which were more sensitive for detecting mild myocardial injury than conventional sequences showed that native T1, T2 and extracellular volume (ECV) values of the LV wall gradually increased from mid-cavity to apex, suggesting gradually worsening myocardial and extracellular matrix edema from mid-ventricle to apex (Figure 4D, E, F).

**Management (medical/interventions)**

Given that her atypical symptoms of acute coronary syndrome had persisted for four days, coronary angiography was electively performed and she received anticoagulant therapy (enoxaparin injection), dual antiplatelet therapy, statin and potassium supplementation. Since a clear diagnosis of TTS, she achieved complete resolution of clinical symptoms with symptomatic treatment 12 days after admission, with significant improvement in cardiac biomarkers.

**Follow-Up:**

At her 1-week follow-up, there was no recurrence of clinical symptoms and a normal TTE. The ECG showed a diffuse deep inverted T wave except V1 and aVL (Figure 1B). At 3 months follow-up, the patient was clinically stable with normal cardiac biomarkers. The ECG showed extensive inversion of T-wave to a lesser extent than at discharge, as well as a normal QTc interval (Figure 1C). Follow-up CMR on day 91 showed a significant improvement in LV function (left ventricular ejection fraction 62%), almost recovery of myocardial dyskinesia with GLS rate of -17.1%, GCS rate of -18.7% and GRS rate of 32.8% (Figure 5A-C). However,
myocardial ECV values remained gradually increased from mid-ventricle to apex, even higher than the first CMR (Figure 5F) and mild LGE was showed on LV anterior, inferior, septal and lateral wall form mid-cavity to apex (Figure 5 G, H), a change rarely seen in previously reported TTS patients. More curiously, both myocardial native T1 and T2 values returned to normal at this time (Figure 5D, E).

Discussion:

We report a patient with typical TTS, and the pathophysiological processes. Our case demonstrates a dynamic ECG evolution of patients with typical TTS, showing ST segment elevation in the acute phase, followed by progressive deep T wave inversion (TWI) with a peak of 2.0 mV in lead V5 observed at around 2-3 weeks. TWI in TTS can be caused by various mechanisms such as epinephrine release, inflammation, myocardial edema, ischemia, oxidative stress and low estrogen hormone levels, but the relevant clinical research is limited. Perazzolo Marra M et al found that the apical to basal gradient of LV myocardial edema detected by CMR was related to TWI which progressed during the acute phase and recovered slowly during the subacute phase in TTS. However, the recovery of myocardial edema in our patient after 3 months did not bring complete recovery of TWI. She had no obvious triggers and showed most of reversible subendocardial perfusion from the changes of CMR, supporting the reversible myocardial microcirculatory disturbance that Leonarda Galiuto and Filippo Crea proposed as the pathophysiological mechanism in primary TTS. Thus, in our case, myocardial edema and ischemia may be the main cause of the deep TWI, and more potential mechanisms deserve to be discussed and explored.

As TTS is a transient manifestation of cardiac disease, myocardial native T1/T2 value and ECV of CMR often tend to normalize in most patients at 3-month follow-up as myocardial edema resolves. However, a curious CMR abnormality was found in this patient’s 3-month follow-up CMR - mild LGE with elevated ECV value but normal native T1 value of the LV apex, the underlying mechanism of which is unknown.

In general, myocardial ECV is elevated because of an increase in extracellular (cardiomyocyte) space relative to intracellular space, such as edema, fibrosis, amyloid deposition in the extracellular space, and these are usually accompanied by an elevated native T1 value. However, T1 and ECV values are not always constant and can vary in different diseases or different processes, they are often combined to accurately identify the nature of the lesion. For example, Sado et al. found a pseudo-normalization phenomenon in Anderson-Fabry disease, where the effects of replacement fibrosis outweigh the fat-related T1 decrease.

Scally et al. found that myocardial energy metabolism was markedly reduced in patients with acute TTS and only partially recovered at 5 months despite complete recovery of myocardial systolic dysfunction, with reduced glucose and regional free fatty acid utilization during the acute phase of TTS. In addition, numerous studies have demonstrated that abnormal lipid metabolism exists in TTS and leads to intramyocardial lipid accumulation, which may contribute to its persistent metabolic dysfunction.

Our patient’s repeat CMR with T1 mapping at 3 months follow up showed a normal T1 value but a persistently elevated ECV. We have no confirmatory evidence to explain this paradox, but a plausible explanation could be intramyocardial lipid deposition due to abnormal lipid metabolism in TTS. On the one hand, the fact that mild LGE was associated with elevated T1 and ECV in this patient suggests myocardial collagen deposition and fibrosis. On the other hand, intramyocardial lipid deposition decreases T1 and counteracts the effect of fibrosis, while probably having no significant influence on ECV. This may be an indication of abnormal lipid metabolism in TTS.

Conclusions

Edema and ischemia may be the main cause of the deep inversion of T wave, and reversible myocardial microcirculatory disturbance exist in TTS. Meanwhile, T1 mapping in CMR showed a normal T1 value but a persistently elevated ECV after TTS full recovery, which is a possible clue to the abnormal lipid metabolism in TTS patients.

Figure Legends:
Figure 1. Initial ECG showed sinus rhythm, ST-segment elevation and positive-negative biphasic T-wave in leads II, III, aVF, V3 and V4, T-wave inversion in lead V5-V6, accompanied by a prolonged QTc interval of 516ms (Figure 1A). ECG at 1-week follow-up (Figure 1B). ECG at 3-month follow-up (Figure 1C).

Figure 2. TTE showed apical ballooning of the LV (A) and myocardial strain showed apical akinesia during the acute phase (B).

Figure 3. Coronary angiography showed no obstructive coronary artery lesions.

Figure 4. CMR during acute phase (day 7). Gradual decrease of left ventricular myocardial strain capacity from basal cavity to apical cavity were showed on bull’s-eye images of longitudinal (A), radial (B) and circumferential (C) strains. LV myocardial native T1 value (D), T2 value (E) and ECV value (F), were also gradually increased from the mid-ventricle to the apex on bull’s-eye images (the normal reference ranges of myocardial T1 value, T2 value, and ECV value are 1192.46 -1226.75 ms, 47.20 -50.62 ms, and 30%, respectively). LGE showed mild enhancement on LV anterior and inferior wall from mid-cavity to apical cavity (G, black triangles). Resting first-pass perfusion imaging showed decreased myocardial perfusion of the anterior, lateral, inferior and infero-septal walls of the apical LV (I, white triangles).

Figure 5. CMR during chronic phase (3 months’ follow up). Significant improvement of LV GLS (A), GRS (B) and GCS (C). Native-T1 and T2 mapping bull’s eye images showed normal myocardial native-T1 and T2 values (D, E). ECV bull’s eye images showed elevated ECV value of the midventricular and apical LV myocardium (F). LGE showed mild enhancement on LV apical, anterior, inferior, septal and lateral wall form mid-cavity to apical cavity (G, H white triangles). Resting first-pass perfusion imaging showed improved myocardial perfusion of LV anterior, lateral, inferior wall (I).

Supplementary material. Supplementary material for CMR parameters.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient.

Conflict of interest: None declared.

Data availability statement: All relevant data are within the manuscript and its Additional files.

References:


