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Gianluca Guarnieri *

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Case Report

Atypical Clinical Presentation of Takotsubo Syndrome in Association with Unusual Clinical onset of Myasthenia Gravis: a Case Report

Gianluca Guarnieri [1,3]*, Michele Della Rocca [2], Alessia Dalla Cia [2], Giancarlo Marenzi [1]

[1]Centro Cardiologico Monzino IRCCS, 20138 Milan, Italy.

[2]Centro Cardiologico Monzino IRCCS, Emergency Department, 20138 Milan, Italy.

[3]Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy.

***Corresponding Author:** Gianluca Guarnieri, Centro Cardiologico Monzino, IRCCS Via Privata Carlo Parea 20138 - Milan (Italy).

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Abstract

Introduction: Takotsubo syndrome (TTS) is a cardiomyopathy triggered by emotional or physical stress. This case report presents a unique instance of TTS associated with myasthenia gravis (MG) in which myasthenic crisis developed after TTS diagnosis and not before.

Case Description: A 73-year-old man presented with difficulty swallowing, dysphonia, and dyspnea, showing moderate-severe left ventricular dysfunction. Blood tests revealed elevated troponin and BNP levels, while the ECG at the arrival showed an ST-elevation in anterior leads. Coronary angiography showed normal aspect of coronary vessels. Echocardiography confirmed TTS with apical ballooning.

After few days, myasthenic symptoms emerged leading to a myasthenic crisis. The patient improved with acetylcholinesterase inhibitors and was discharged with pyridostigmine and prednisone. Follow-up revealed complete resolution of left ventricular dysfunction.

Discussion: MG rarely affects the heart, but in this case, it led to TTS. Notably, TTS occurred before the myasthenic crisis, emphasizing the need for cardiac monitoring in patients with new neurological diagnoses and acute respiratory.

Keywords: takotsubo; myasthenia gravis; myasthenic crisis

Introduction

Takotsubo syndrome (TTS) is a cardiomyopathy that consists in transient abnormalities in myocardial motion that may result in left ventricle disfunction[1] (LVD). This condition is generally induced by emotional or physical stress factors and it is also known as the 'The broken heart syndrome' [2].

TTS was firstly described in Japan and it is reported to represent almost one to two % of all patients who present positive troponin and chest pain suspected of acute coronary syndrome (ACS).

It occurs more frequently in women. Moreover, most of patients are older than 50 years of age at the time of the diagnosis. Data from the literature show a 30-days mortality about 4% that is comparable to patients with ACS. At the same time, long term risk of death in TTS is still similar[3] or even higher than what observed in ACS. Furthermore, survivors of TTS have increased risk of hospitalization due to heart failure than general population, but lower to survivors of ACS [4].

Stress factors

In TTS, a stress factor may be identified in almost 85% of cases; it could be either emotional or physical. Among emotional factors, grief, anger or relationship conflicts are the most frequent;

Physical stressor include surgery, chemotherapy, stroke, asthma or neurological disease [5].

The investigation of the stress factors may play a crucial role; in fact, patients who have a physical stressor are more likely to be haemodynamically unstable with worse LV function, higher incidence of cardiogenic shock compared to patients who have emotional trigger[6]. In

particular, there is growing evidence of the fact that patients with TTS with concomitant neurological disease may present greater myocardial damage and more pronounced LVD[7]. Furthermore, some studies indicate the presence of critical illness as the most important determinant of both in-hospital[8] mortality and long term outcome [9]. Specifically, a worse survival rate is observed in TTS consequent to neurological disorders [10].

Among neurological diseases as possible triggers, seizures, intracranial hemorrhage and cerebral ischemia are the most frequent ones. Moreover, TTS has been occasionally reported in association with neuromuscular disorder as myasthenia gravis (MG) or Guillain Barrè syndrome[11].

In this case report, we present an unusual case of MG-related TTS, and at our best knowledge, this is the first in which myasthenic crisis developed approximately two days after TTS diagnosis and not before.

Case description

Our patients is a 73-years-old man who came to our attention due to difficulty swallowing solid foods for about 20 days, worsened in the last 3 days with the onset of dysphonia and difficulty swallowing liquids. The patient also reported occasional paroxysmal dyspnea episodes that resolved after food vomiting. Of note, he had always been asymptomatic for chest pain. The patient had no significant medical history, except for borderline hypertension under investigation.

He had no family history of cardiovascular disease, but his mother was affected by MG.

On arrival at the emergency room, the patient was markedly anxious, complaining of globus sensation in his throat. He was subjectively eupneic and asymptomatic for chest pain. There was mild dysphonia and abundant drooling. Blood pressure was normal and the hemodynamic status was stable, but with a tendency towards sinus tachycardia (HR 120 bpm).

Physical examination showed normal peripheral perfusion and normal findings throughout the body except for mild crackles at the base of the right lung; no signs of congestive heart failure were present. The physical examination did not show any obvious focal neurological sign.

An arterial blood sample showed mild hypoxemia and mild hypocapnia (pCO2 36 mmHg, pO2 65 mmHg), with a pH within the normal range and a slightly reduced peripheral oxygen saturation (SatO2 95%). The rapid antigen test for SARS-CoV-2 was negative.

Venous blood tests showed an increase in inflammation indices with CRP 145 mg/L and neutrophilic leukocytosis (WBC 18,600/mm3 with neutrophils 16,160/mm3 – 87%), normal values of renal function and plasma electrolytes. The atrial natriuretic peptide type B (BNP) and the markers of myocardial necrosis (high-sensitivity troponin I, hsTnI) were elevated (538 pg/mL and 2363 ng/L, respectively). The D-dimer value was within the normal range for age.

In light of the initial data showing high levels of hsTnI and BNP, we performed an ECG (shown in Figure 1) and a transthoracic echocardiogram (Figure 2). The ECG showed sinus tachycardia, left axis deviation, and ST-elevation in anterior leads (V2-V3).

The transthoracic echocardiogram showed apical akinesis with moderate to severe LVD; there were no pathological findings in the thoracic aorta, cardiac valves or right ventricle, and there was no pericardial effusion. A contrast-enhanced echocardiogram (Luminity) ruled out the presence of intracardiac thrombotic formations (Figure 3).

In consideration of the atypical characteristics of the patient's symptoms, a baseline CT scan (brain and thorax) was performed to rule out an acute neurological etiology. The brain CT showed a mild picture of non-specific chronic vascular leukoencephalopathy and ruled out the presence of radiological signs related to acute lesions (ischemic, embolic, or hemorrhagic). The thoracic CT showed a focal consolidation of the middle and lower right lung lobe with ground glass opacities, compatible with pneumonia (likely *aspiration pneumonia*). Additionally, the exam ruled out the presence of anatomical anomalies and extrinsic compression phenomena affecting the esophagus and trachea.

Despite the presence of atypical symptoms, the preliminary exams suggested the presence of acute coronary syndrome with moderate to severe LVD, whose clinical onset could not be properly identified due to the absence of chest pain or ischemic equivalents. Therefore, immediate admission to our Coronary Intensive Care Unit was arranged.

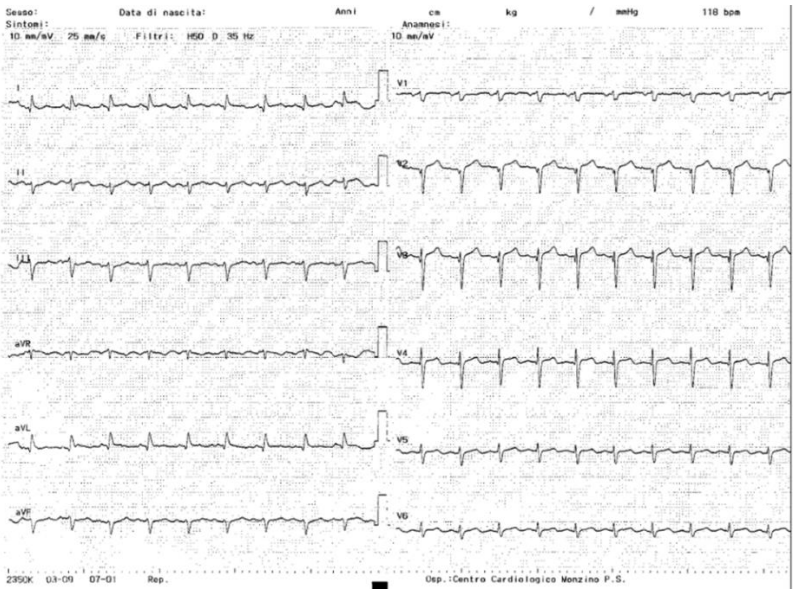

Figure 1: ECG at arrival at the emergency department

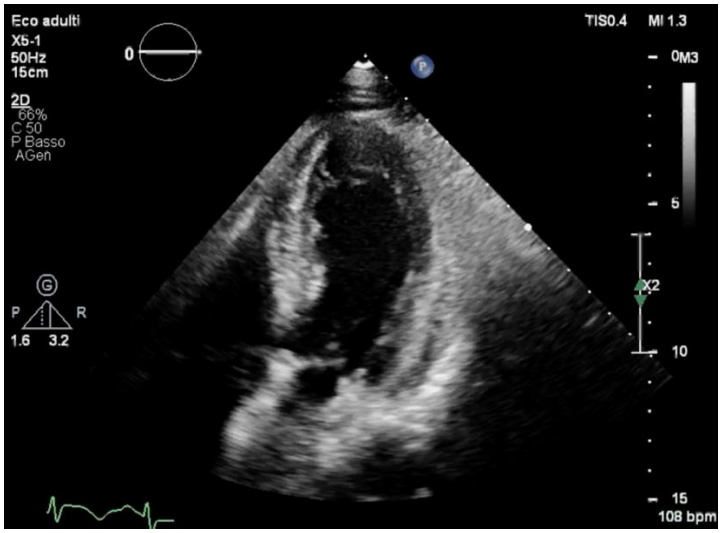

Figure 2: Echocardiogram showing apical ballooning

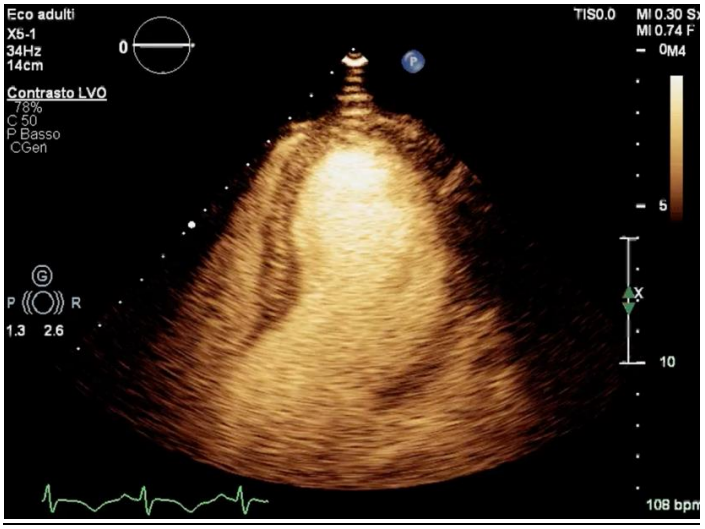

Figure 3: Echocardiogram with contrast agent showing the absence of thrombotic apposition in cardiac apex

Management

Due to the concomitant pneumonia documented on chest CT, a dual empirical antibiotic therapy (Ceftriaxone and Azithromycin) and oxygen therapy was administered during hospitalization. During the first days of admission, a worsening of hypoxemia and the onset of paroxysmal respiratory distress with severe desaturation was observed, which required the intermittent use of cycles of non-invasive ventilation with oro-facial mask (BiPAP). Notably, the dyspnea mainly occurred when the patient accumulated excessive saliva that he was unable to swallow, requiring multiple external aspirations to remove secretions. The symptoms onset, characterized by dysphagia and dysphonia, showed a significant worsening during hospitalization, leading to complete inability to self-nourishing; therefore, a nasogastric tube was inserted and total enteral nutrition was administered. Ivabradine and continuous infusion beta-blockers were administered to reduce heart rate and oxygen consumption.

A low dose of intravenous furosemide was administered in order to achieve an adequate urine output rate and maintain hemodynamic stability.

On the second day of hospitalization, a contrast-enhanced CT scan was performed, which confirmed the absence of acute brain lesions, stenosis or occlusions of the major intracranial vessels, extrinsic esophago-tracheal compression, and intracardiac thrombosis. In addition, the coronary arterial circulation was investigated, which was found to be free from significant lesions except for an atheromatous plaque in the anterior descending artery causing stenosis that could not be accurately quantified due to technical artifacts.

Therefore, it was decided to proceed with coronary angiography, which showed no relevant stenosis of the major epicardial vessels (Figure 3).

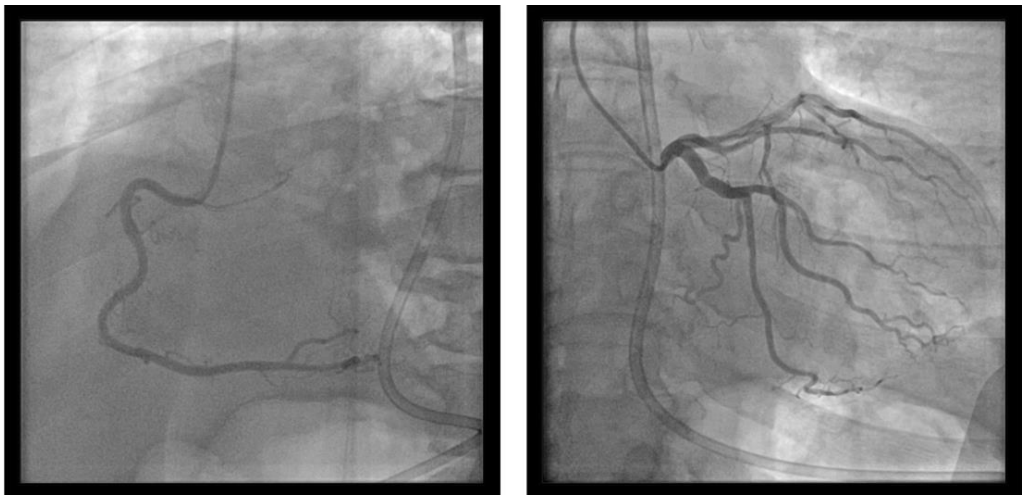

Figure 4: Coronary angiography showing the absence of obstructive stenosis

A trans-thoracic echocardiogram was repeated and confirmed the presence of moderate-to-severe reduction in left ventricular systolic function with apical ballooning and compensatory hyperkinesia of the basal segments, consistent with the diagnosis of Takotsubo Syndrome. During hospitalization, serial ECG monitoring showed ischemic evolution with the appearance of biphasic/negative T waves in the anterolateral and inferior leads and prolonged QT interval duration (QTc 500-510 ms). No significant arrhythmias were documented on ECG monitoring. Serial laboratory tests showed progressive normalization of inflammation indices and cardiac necrosis enzymes (peak hsTnI = 3184 ng/L).

In addition to the cardiological investigations, a neurological specialist evaluation was performed, which documented dysarthric speech, asymmetry of the eyelid, and slight exhaustion in motor tests (tongue protrusion, head flexion, Mingazzini I and II). Therefore, a concomitant neuromuscular plaque pathology was suspected (mainly consistent with Myasthenia Gravis). Therefore, the patient was referred to General Intensive Care Unit.

The repetitive nerve stimulation test confirmed MG diagnosis and high levels of acetylcholine receptor antibodies were detected. So, a therapy with an acetylcholinesterase inhibitor was started with rapid improvement of the patient's clinical condition.

Patient was discharged on pyridostigmine and prednisone.

After two months a trans-thoracic echocardiogram revealed a complete resolution of the LVD.

Discussion

MG is a rarely condition in men and occurs with cardiac involvement in almost 16% of patients; arrhythmic disorders, pericarditis and myocarditis have been described as the most frequent and, rarely, MG could lead to TTS. Data from the National Inpatient Sample databased provides a prevalence of 0.3% of MG-related TTS.

Rathish et Al shown that MG in patients with TTS may present in various forms; respiratory involvements is the prevalent (81%), followed by blepharoptosys (63%), and limb muscle weakness (50%); myasthenic crisis is described in some cases[12].

In most of cases in which MG present with LVD the diagnosis is represented by myocarditis and in almost the whole cases antibodies towards heart muscle may be detected.

The differential diagnosis between myocarditis and TS could be made thank to cardiac MRI showing the presence of late contrast enhancement in the first case. In our case, patient could not undergo cardiac MRI

because we needed to transfer him in a hospital with neurological department.

However, accordingly with the International Takotsubo Diagnostic Criteria (InterTAK diagnostic criteria), TS was the most likely diagnosis.

Correspondingly to literature, myasthenic crisis has emerged as a stress factor of TS. Moreover, when TS is concomitant to myasthenic crisis higher rate of mortality is described[13].

So, to our opinion, every patient with a new diagnosis of neurological disorder with acute respiratory condition should undergo close cardiac monitoring and serial ECG.

Nevertheless, to our best knowledge, our case is the first case in which TS occurs before myasthenic crisis presentation. So, similarly, patients with stress- induced cardiomyopathy in absence of emotional trigger should undergo neurological investigations. In fact, neurological screening may prevent life-threatening complication including myasthenic crisis.

Lastly, we suppose that there is a strong necessity to continue to report cases of myasthenic crisis and TS to improve the competence of make diagnosis earlier and start a life-saving therapy earlier.

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