

## A case report of myocardial inflammation in takotsubo syndrome. A chicken-or-the-egg phenomenon

### ARTICLE INFO

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Takotsubo syndrome can typically present as acute heart failure associated with significant wall motion abnormalities and left ventricular dysfunction that is reversible in the majority of cases. Although left ventricular apical ballooning is the predominant manifestation, other types such as midventricular, basal and focal type have been described [1–3].

We describe the case of a 76-year-old woman presenting to the emergency department with acute dyspnea and angina pectoris. Importantly, the patient experienced an episode of severe bronchitis 2 weeks prior to presentation to our emergency department and reported a functional decline and decreased exercise capacity since then.

Her past medical history further included arterial and pulmonary hypertension, moderate aortic and mitral valve regurgitation, atrial fibrillation, multiple complex radiofrequency ablations, and a pacemaker for cavotricuspid isthmus block. On physical exam, the patient's heart rate was 90 bpm and her blood pressure 120/70 mmHg. Auscultation revealed a systolic murmur (II/VI) and clear lung fields (no crackles, rales or wheezes). There were no signs of peripheral edema.

Initial laboratory tests revealed an elevated NT-proBNP of 2287 ng/L and peak high-sensitivity troponin T of 229 ng/L. Furthermore, chest X-ray revealed pulmonary edema. Electrocardiogram (ECG) revealed intermittent atrial and ventricular pacing, as well as T-wave inversions in II, III, aVF and V4-V6 (Fig. 1, a).

Given the initial clinical presentation, ECG findings, and troponin elevation, the differential diagnosis included Non-ST-segment elevation myocardial infarction (NSTEMI), stress or Takotsubo cardiomyopathy, myopericarditis, and myocarditis.

First, transthoracic echocardiography depicted left ventricular apical and septal hypokinesis, right ventricular dysfunction, severely dilated atria, moderately reduced left ventricular ejection fraction (LVEF 38%), aortic regurgitation, moderate to severe mitral regurgitation, mild tricuspid regurgitation and an increased pulmonary artery systolic pressure (PASP 42 mmHg) (Fig. 1, b). Coronary angiography revealed mild coronary sclerosis in the left anterior descending artery and myocardial bridging. Moreover, left ventricular angiography showed a moderately reduced left ventricular function with a left ventricular end-diastolic pressure (LVEDP) of 17 mmHg (normal 6–12 mmHg) and

“apical ballooning”, suggesting the diagnosis of takotsubo syndrome (Fig. 1, c).

The patient improved with standard heart failure therapy and was transferred from the intensive care unit to the inpatient ward on day 4. Repeat echocardiography at that time revealed a nearly recovered LVEF of 50%. Within days, left ventricular systolic function returned to normal, while regional wall motion abnormalities as septal hypokinesis remained. In contrast, right ventricular function remained moderately decreased with elevated PASP of 63 mmHg. During the following days, the patient was hemodynamically stable with absence of cardiac arrhythmias on telemetry monitoring.

When the patient was asked about any events that may have triggered her stress induced cardiomyopathy, she explained that she did not experience any extraordinary life events during the last few months [4–6]. Also, she did not have any known neurologic or psychiatric disorders and no major illnesses. Given the absence of classic risk factors for takotsubo syndrome and the fact that the patient continued to have episodes of chest pain and functional decline after an episode of severe bronchitis, she underwent dedicated imaging to evaluate for myocardial inflammation. Positron emission tomography – computed tomography (PET-CT) was chosen as the preferred imaging method over cardiac magnetic resonance imaging (CMR), since the patient had a pacemaker that was not compatible with CMR. PET CT revealed increased myocardial glucose uptake in the anteroseptal region consistent with regional myocardial inflammation (Fig. 1, d).

During treatment with standard heart failure therapy, the patient experienced significant improvement of functional capacity and clinical symptoms. As the PET-CT showed an inflammatory component of takotsubo cardiomyopathy, the patient was advised to only perform light physical activity for three months. At 3-months follow-up, the patient's symptoms had improved.

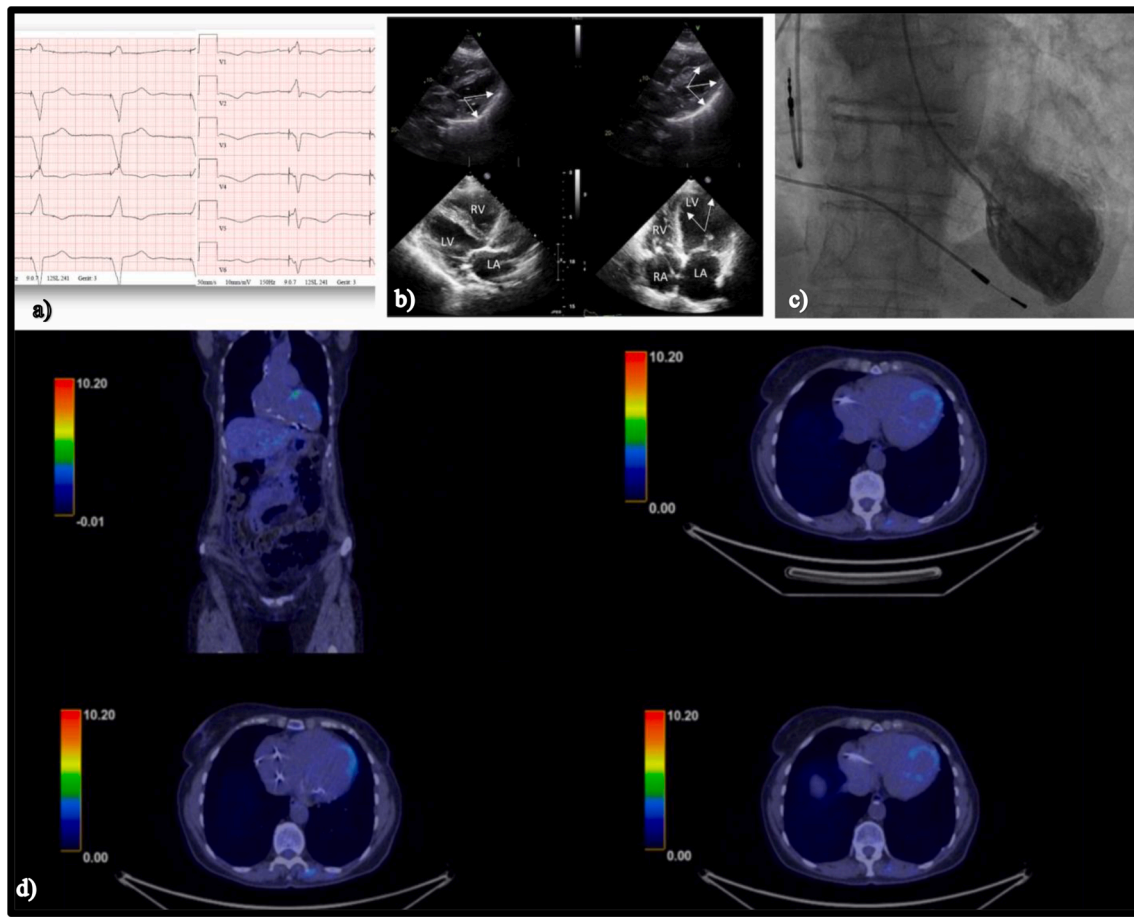
Finally, our patient was diagnosed with takotsubo syndrome and myocardial inflammation. Whether myocardial inflammation caused the manifestation of takotsubo syndrome, or myocardial inflammation was a bystander of takotsubo cardiomyopathy, remains to be determined in future research. Scally and colleagues identified myocardial inflammatory infiltrates of macrophages and an increase in systemic

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**Fig. 1.** (a): Electrocardiogram (ECG) on hospital admission. (b): Initial transthoracic echocardiography, (c): Ventriculogram: Apical ballooning, (d): Positron emission tomography – computed tomography (PET-CT): Dilated left ventricle with increased anteroseptal glucose uptake suggestive of inflammation.

pro-inflammatory cytokines in patients with takotsubo syndrome. In their study, the team acknowledged that it is not possible to conclude, whether inflammation is a cause or consequence of the acute takotsubo event [7]. Although the exact pathophysiology is still unclear, sympathetic hyperactivation, catecholamine excess and myocardial stunning are considered relevant factors [1,8]. It is presumed that a combination of high catecholamine levels and an excess activation of beta-adrenergic receptors (BARs) might contribute to apoptosis and necrosis due to high concentrations of oxidative stress, calcium overload and microcirculatory disturbance [1,2].

The occurrence of moderately elevated cardiac enzymes provides evidence for myocardial damage. Moreover, injured myocytes were found in several specimens obtained from autopsies of takotsubo syndrome [9]. An experimental model of takotsubo cardiomyopathy demonstrated a regional and temporal inflammatory response with a predominance of proinflammatory macrophages and an insufficient switch to anti-inflammatory/tissue reparative macrophages. Similar outcomes were found in human post-mortem cases. This may indicate that sympathetic overreaction results in myocardial tissue injury including local inflammation and intramyocardial edema, which could be interpreted as catecholamine induced chemical myocarditis [3,10,8,11].

Eventually myocardial inflammation might be an essential element in the wide clinical spectrum of takotsubo syndrome. Numerous preceding physical stressors have been described to be associated with the development of takotsubo syndrome. Severe bacterial, viral or other infectious diseases causing acute myocarditis are also considered as strong physical stressors possibly provoking the syndrome [2,8,11].

Differentiating myocarditis from takotsubo syndrome appears to be

challenging due to their related clinical phenotype and the fact that myocardial inflammation has been increasingly reported in the context of takotsubo syndrome.

In summary, we conclude based on our observation and previous reports in the literature that takotsubo syndrome may be associated with local and systemic inflammatory response, hence modulators of inflammation may be a potential therapeutic target in patients who do not recover with standard heart failure therapy.

#### Ethical approval and consent to participate

Ethical approval was not necessary for this descriptive case report. Data for this case report has been collected after written informed consent of the patient and in accordance with the Declaration of Helsinki.

#### Consent for publication

The authors confirm that written consent for publication of this case report and any accompanying images has been obtained from the patient. A copy of the written consent is available for review by the Editor of this journal.

#### Availability of data and materials

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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## Authors' contributions

A.Rr. has drafted the manuscript, S.G contributed in the writing, U.L und B.H. have critically appraised, revised and approved the content of the manuscript. All authors read and approved the final manuscript.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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